(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

CORRECTED VERSION

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
5 December 2002 (05.12.2002)

PCT

(10) International Publication Number
WO 02/096268 A2

(51) International Patent Classification[7]: A61B

(21) International Application Number: PCT/US02/16945

(22) International Filing Date: 28 May 2002 (28.05.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/293,488	25 May 2001 (25.05.2001)	US
60/363,527	12 March 2002 (12.03.2002)	US
60/380,695	14 May 2002 (14.05.2002)	US
60/380,692	14 May 2002 (14.05.2002)	US

(63) Related by continuation (CON) or continuation-in-part (CIP) to earlier applications:

US	60/293,488 (CIP)
Filed on	25 May 2001 (25.05.2001)
US	60/363,527 (CIP)
Filed on	12 March 2002 (12.03.2002)
US	60/380,695 (CIP)
Filed on	14 May 2002 (14.05.2002)
US	60/380,692 (CIP)
Filed on	14 May 2002 (14.05.2002)

(71) Applicant *(for all designated States except US)*: **IMAGING THERAPEUTICS** [US/US]; 1720 South Amphlett Boulevard, Suite 240, San Mateo, CA 94402 (US).

(72) Inventors; and

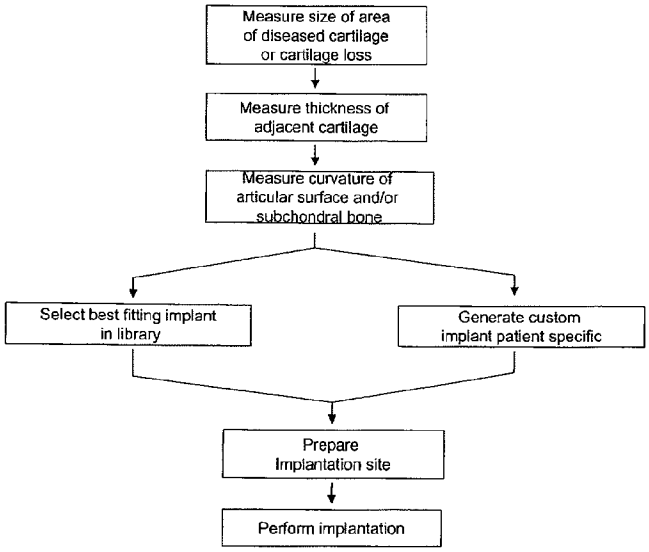
(75) Inventors/Applicants *(for US only)*: **LANG, Philipp** [DE/US]; 36 Fairlawn Lane, Lexington, MA 02420 (US). **LINDER, Barry** [US/US]; 29 Bluehaven Court, Danville, CA 94506 (US). **STEINES, Daniel** [DE/US]; 3619 Park Boulevard, Palo Alto, CA 94306 (US).

(74) Agents: **PASTERNAK, Dahna, S.** et al.; Robins & Pasternak LLP, 545 Middlefield Road, Suite 180, Menlo Park, CA 94025 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,

[Continued on next page]

(54) Title: METHODS AND COMPOSITIONS FOR ARTICULAR RESURFACING



(57) Abstract: Disclosed herein are methods and compositions for producing articular repair materials and for repairing an articular surface. In particular, methods for providing articular replacement material, the method comprising the step of producing articular replacement material of selected size, curvature and/or thickness are provided. Also provided are articular surface repair systems designed to replace a selected area cartilage, for example, a system comprising at least one solid, non-pliable component and an external surface having near anatomic alignment to the surrounding structures.

WO 02/096268 A2

CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *without international search report and to be republished upon receipt of that report*

(48) Date of publication of this corrected version:
10 April 2003

(15) Information about Correction:
see PCT Gazette No. 15/2003 of 10 April 2003, Section II

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

METHODS AND COMPOSITIONS FOR ARTICULAR RESURFACING

Cross-Reference to Related Applications

This application claims the benefit of U.S. Serial Number 60/293,488 entitled "METHODS TO IMPROVE CARTILAGE REPAIR SYSTEMS", filed May 25, 2001, U.S. Serial Number 60/363,527, entitled "NOVEL DEVICES FOR CARTILAGE REPAIR, filed March 12, 2002 and U.S. Serial Numbers 60/380,695 and Unassigned, entitled "METHODS AND COMPOSITIONS FOR CARTILAGE REPAIR," (Attorney Docket Number 6750-0005p2) and "METHODS AND COMPOSITIONS FOR JOINT REPAIR," (Attorney Docket Number 6750-0005p3), filed May 14, 2002, all of which applications are hereby incorporated by reference in their entireties.

Technical Field

The present invention relates to orthopedic methods, systems and prosthetic devices and more particularly relates to methods, systems and devices for articular resurfacing.

Background

There are various types of cartilage, e.g., hyaline cartilage and fibrocartilage. Hyaline cartilage is found at the articular surfaces of bones, e.g., in the joints, and is responsible for providing the smooth gliding motion characteristic of moveable joints. Articular cartilage is firmly attached to the underlying bones and measures typically less than 5mm in thickness in human joints, with considerable variation depending on joint and site within the joint. In addition, articular cartilage is aneural, avascular, and alymphatic. In adult humans, this cartilage derives its nutrition by a double diffusion system through the synovial membrane and through the dense matrix of the cartilage to reach the chondrocyte, the cells that are found in the connective tissue of cartilage.

Adult cartilage has a limited ability of repair; thus, damage to cartilage produced by disease, such as rheumatoid and/or osteoarthritis, or trauma can lead to serious physical deformity and debilitation. Furthermore, as human articular cartilage

ages, its tensile properties change. The superficial zone of the knee articular cartilage exhibits an increase in tensile strength up to the third decade of life, after which it decreases markedly with age as detectable damage to type II collagen occurs at the articular surface. The deep zone cartilage also exhibits a progressive decrease in tensile strength with increasing age, although collagen content does not appear to decrease. These observations indicate that there are changes in mechanical and, hence, structural organization of cartilage with aging that, if sufficiently developed, can predispose cartilage to traumatic damage.

Usually, severe damage or loss of cartilage is treated by replacement of the joint with a prosthetic material, for example, silicone, e.g. for cosmetic repairs, or metal alloys. See, *e.g.*, U.S. Patent No. 6,383,228, issued May 7, 2002; U.S. Patent No. 6,203,576, issued March 20, 2001; U.S. Patent No. 6,126,690, issued October 3, 2000. Implantation of prosthetic devices is usually associated with loss of underlying tissue and bone without recovery of the full function allowed by the original cartilage. Serious long-term complications associated with the presence of a permanent foreign body can include infection, osteolysis and also loosening of the implant.

Further, joint arthroplasties are highly invasive and require surgical resection of the entire or the majority of the articular surface of one or more bones. With these procedures, the marrow space is reamed in order to fit the stem of the prosthesis. The reaming results in a loss of the patient's bone stock.

Osteolysis will frequently lead to loosening of the prosthesis. The prosthesis will subsequently have to be replaced. Since the patient's bone stock is limited, the number of possible replacement surgeries is also limited for joint arthroplasty. In short, over the course of 15 to 20 years, and in some cases shorter time periods, the patients may run out of therapeutic options resulting in a very painful, non-functional joint.

The use of matrices, tissue scaffolds or other carriers implanted with cells (*e.g.*, chrondrocytes, chondrocyte progenitors, stromal cells, mesenchymal stem cells, etc.) has also been described as a potential treatment for cartilage repair. See, also, International Publications WO; 99/51719; WO 01/91672 and WO 01/17463;U.S. Patent No. 5,283,980 B1, issued September 4, 2001; U.S. Patent No. 5,842,477, issued December 1, 1998; U.S. Patent No. 5,769,899, issued June 23, 1998; U.S.

Patent No. 4,609,551, issued Sep. 2, 1986; U.S. Patent No. 5,041,138, issued Aug. 20, 199; U.S. Patent No. 5,197,985, issued March 30, 1993; U.S. Patent No. 5,226,914, issued July13, 1993; U.S. Patent No. 6,328,765, issued December 11, 2001; U.S. Patent No. 6,281,195, issued August 28, 2001; and U.S. Patent No. 4,846,835, issued July 11, 1989. However, clinical outcomes with biologic replacement materials such as allograft and autograft systems and tissue scaffolds have been uncertain since most of these materials cannot achieve a morphologic arrangement or structure similar to or identical to that of normal, disease-free human tissue. Moreover, the mechanical durability of these biologic replacement materials is not certain.

Despite the large number of studies in the area of cartilage repair, the integration of the cartilage replacement material with the surrounding cartilage of the patient has proven difficult. In particular, integration can be extremely difficult due to differences in thickness and curvature between the surrounding cartilage and/or the underlying subchondral bone and the cartilage replacement material.

Thus, there remains a need for methods and compositions for joint repair, including methods and compositions that facilitate the integration between the cartilage replacement system and the surrounding cartilage.

Summary

The present invention provides novel devices and methods for replacing a portion (*e.g.*, diseased area and/or area slightly larger than the diseased area) of a joint (*e.g.*, cartilage and/or bone) with a non-pliable, non-liquid (*e.g.*, hard) implant material, where the implant achieves a near anatomic fit with the surrounding structures and tissues. In cases where the devices and/or methods include an element associated with the underlying articular bone, the invention also provides that the bone-associated element achieves a near anatomic alignment with the subchondral bone. The invention also provides for the preparation of an implantation site a single cut.

In one aspect, the invention includes a method for providing articular replacement material, the method comprising the step of producing articular replacement (*e.g.*, cartilage replacement material) of selected dimensions (*e.g.*, size, thickness and/or curvature).

In another aspect, the invention includes a method of making cartilage repair material, the method comprising the steps of (a) measuring the dimensions (*e.g.*, thickness, curvature and/or size) of the intended implantation site or the dimensions of the area surrounding the intended implantation site; and (b) providing cartilage replacement material that conforms to the measurements obtained in step (a). In certain aspects, step (b) comprises measuring the thickness of the cartilage surrounding the intended implantation site and measuring the curvature of the cartilage surrounding the intended implantation site. In other embodiments, step (a) comprises measuring the size of the intended implantation site and measuring the curvature of the cartilage surrounding the intended implantation site. In other embodiments, step (a) comprises measuring the thickness of the cartilage surrounding the intended implantation site, measuring the size of the intended implantation site, and measuring the curvature of the cartilage surrounding the intended implantation site.

In any of the methods described herein, or more components of the articular replacement material (*e.g.*, the cartilage replacement material) is non-pliable, non-liquid, solid or hard. The dimensions of the replacement material may be selected following intraoperative measurements, for example measurements made using imaging techniques such as ultrasound, MRI, CT scan, x-ray imaging obtained with x-ray dye and fluoroscopic imaging. A mechanical probe (with or without imaging capabilities) may also be used to selected dimensions, for example an ultrasound probe, a laser, an optical probe and a deformable material.

In any of the methods described herein, the replacement material may be selected (for example, from a pre-existing library of repair systems), grown from cells and/or hardened from various materials. Thus, the material can be produced pre- or post-operatively. Furthermore, in any of the methods described herein the repair material may also be shaped (*e.g.*, manually, automatically or by machine), for example using mechanical abrasion, laser ablation, radiofrequency ablation, cryoablation and/or enzymatic digestion.

In any of the methods described herein, the articular replacement material may comprise synthetic materials (*e.g.*, metals, polymers, alloys or combinations thereof) or biological materials such as stem cells, fetal cells or chondrocyte cells.

In another aspect, the invention includes a method of repairing a cartilage in a subject, the method of comprising the step of implantating cartilage repair material prepared according to any of the methods described herein.

In yet another aspect, the invention provides a method of determining the curvature of an articular surface, the method comprising the step of (a) intraoperatively measuring the curvature of the articular surface using a mechanical probe. The articular surface may comprise cartilage and/or subchondral bone. The mechanical probe (with or without imaging capabilities) may include, for example an ultrasound probe, a laser, an optical probe and/or a deformable material.

In a still further aspect, the invention provides a method of producing an articular replacement material comprising the step of providing an articular replacement material that conforms to the measurements obtained by any of the methods of described herein.

In a still further aspect, the invention includes a partial articular prosthesis comprising a first component comprising a cartilage replacement material; and a second component comprising one or more metals, wherein said second component has a curvature similar to subchondral bone, wherein said prosthesis comprises less than about 80% of the articular surface. In certain embodiments, the first and/or second component comprises a non-pliable material (*e.g.*, a metal, a polymer, a metal allow, a solid biological material). Other materials that may be included in the first and/or second components include polymers, biological materials, metals, metal alloys or combinations thereof. Furthermore, one or both components may be smooth or porous (or porous coated). In certain embodiments, the first component exhibits biomechanical properties (*e.g.*, elasticity, resistance to axial loading or shear forces) similar to articular cartilage. The first and/or second component can be bioresorbable and, in addition, the first or second components may be adapted to receive injections.

In another aspect, a partial articular prosthesis comprising an external surface located in the load bearing area of an articular surface, wherein the dimensions of said external surface achieve a near anatomic fit with the adjacent cartilage is provided. The prosthesis of may further comprise one or more metals or metal alloys.

In yet another aspect, an articular repair system comprising (a) cartilage replacement material, wherein said cartilage replacement material has a curvature similar to surrounding or adjacent cartilage; and (b) at least one non-biologic material, wherein said articular surface repair system comprises a portion of the articular surface equal to or smaller than the weight-bearing surface is provided. In certain embodiments, the cartilage replacement material is non-pliable (*e.g.*, hard hydroxyapatite, etc.). In certain embodiments, the system exhibits biomechanical (*e.g.*, elasticity, resistance to axial loading or shear forces) and/or biochemical properties similar to articular cartilage. The first and/or second component can be bioresorbable and, in addition, the first or second components may be adapted to receive injections.

In a still further aspect of the invention, an articular surface repair system comprising a first component comprising a cartilage replacement material, wherein said first component has dimensions similar to that of adjacent or surrounding cartilage; and a second component, wherein said second component has a curvature similar to subchondral bone, wherein said articular surface repair system comprises less than about 80% of the articular surface (*e.g.*, a single femoral condyle, tibia, etc.) is provided. In certain embodiments, the first component is non-pliable (*e.g.*, hard hydroxyapatite, etc.). In certain embodiments, the system exhibits biomechanical (*e.g.*, elasticity, resistance to axial loading or shear forces) and/or biochemical properties similar to articular cartilage. The first and/or second component can be bioresorbable and, in addition, the first or second components may be adapted to receive injections. In certain embodiments, the first component has a curvature and thickness similar to that of adjacent or surrounding cartilage. The thickness and/or curvature may vary across the implant material.

In a still further embodiment, a partial articular prosthesis comprising (a) a metal or metal alloy; and (b) an external surface located in the load bearing area of an articular surface, wherein the external surface designed to achieve a near anatomic fit with the adjacent cartilage is provided.

Any of the repair systems or prostheses described herein (*e.g.*, the external surface) may comprise a polymeric material, for example attached to said metal or metal alloy. Further, any of the systems or prostheses described herein can be adapted

to receive injections, for example, through an opening in the external surface of said cartilage replacement material (*e.g.*, an opening in the external surface terminates in a plurality of openings on the bone surface). Bone cement, therapeutics, and/or other bioactive substances may be injected through the opening(s). In certain embodiments, bone cement is injected under pressure in order to achieve permeation of portions of the marrow space with bone cement.

These and other embodiments of the subject invention will readily occur to those of skill in the art in light of the disclosure herein.

Brief Description of the Figures

FIG. 1 is a flowchart depicting various methods of the present invention including, measuring the size of an area of diseased cartilage or cartilage loss, measuring the thickness of the adjacent cartilage, and measuring the curvature of the articular surface and/or subchondral bone. Based on this information, a best fitting implant can be selected from a library of implants or a patient specific custom implant can be generated. The implantation site is subsequently prepared and the implantation is performed.

FIG. 2 is a color reproduction of a three-dimensional thickness map of the articular cartilage of the distal femur. Three-dimensional thickness maps can be generated, for example, from ultrasound, CT or MRI data. Dark holes within the substances of the cartilage indicate areas of full thickness cartilage loss.

FIG. 3 shows an example of a Placido disc of concentrically arranged circles of light.

FIG. 4 shows an example of a projected Placido disc on a surface of fixed curvature.

FIG. 5 shows an example of a 2D color-coded topographical map of an irregularly curved surface.

FIG. 6 shows an example of a 3D color-coded topographical map of an irregularly curved surface.

FIG. 7 shows a reflection resulting from a projection of concentric circles of light (Placido Disk) on each femoral condyle, demonstrating the effect of variation in surface contour on the reflected circles.

FIG. 8A-H are schematics of various stages of knee resurfacing. **FIG. 8A** shows an example of normal thickness cartilage in the anterior, central and posterior portion of a femoral condyle **800** and a cartilage defect **805** in the posterior portion of the femoral condyle. **FIG. 8B** shows an imaging technique or a mechanical, optical, laser or ultrasound device measuring the thickness and detecting a sudden change in thickness indicating the margins of a cartilage defect **810**. **FIG. 8C** shows a weight-bearing surface **815** mapped onto the articular cartilage. Cartilage defect **805** is located within the weight-bearing surface **815**. **FIG. 8D** shows an intended implantation site (stippled line) **820** and cartilage defect **805**. The implantation site **820** is slightly larger than the area of diseased cartilage **805**. **FIG. 8E** depicts placement of a single component articular surface repair system **825**. The external surface of the articular surface repair system **826** has a curvature similar to that of the surrounding cartilage **800** resulting in good postoperative alignment between the surrounding normal cartilage **800** and the articular surface repair system **825**. **FIG. 8F** shows an exemplary multi-component articular surface repair system **830**. The distal surface of the deep component **832** has a curvature similar to that of the adjacent subchondral bone **835**. The external surface of the superficial component **837** has a thickness and curvature similar to that of the surrounding normal cartilage **800**. **FIG. 8G** shows an exemplary single component articular surface repair system **840** with a peripheral margin **845** substantially non-perpendicular to the surrounding or adjacent normal cartilage **800**. **FIG. 8H** shows an exemplary multi-component articular surface repair system **850** with a peripheral margin **845** substantially non-perpendicular to the surrounding or adjacent normal cartilage **800**.

FIG. 9, A through **E**, are schematics depicting exemplary knee imaging and resurfacing. **FIG. 9A** is a schematic depicting a magnified view of an area of diseased cartilage **905** demonstrating decreased cartilage thickness when compared to the surrounding normal cartilage **900**. The margins **910** of the defect have been determined. **FIG. 9B** is a schematic depicting measurement of cartilage thickness **915** adjacent to the defect **905**. **FIG. 9C** is a schematic depicting placement of a multi-component mini-prosthesis **915** for articular resurfacing. The thickness **920** of the superficial component **923** closely approximates that of the adjacent normal cartilage **900** and varies in different regions of the prosthesis. The curvature of the distal

portion of the deep component **925** is similar to that of the adjacent subchondral bone **930**. **FIG. 9D** is a schematic depicting placement of a single component mini-prosthesis **940** utilizing fixturing stems **945**. **FIG. 9E** depicts placement of a single component mini-prosthesis **940** utilizing fixturing stems **945** and an opening **950** for injection of bone cement **955**. The mini-prosthesis has an opening at the external surface **950** for injecting bone cement **955** or other liquids. The bone cement **955** can freely extravasate into the adjacent bone and marrow space from several openings at the undersurface of the mini-prosthesis **960** thereby anchoring the mini-prosthesis.

FIG. 10A to **C**, are schematics depicting other exemplary knee resurfacing devices and methods. **FIG 10A** is a schematic depicting normal thickness cartilage in the anterior and central and posterior portion of a femoral condyle **1000** and a large area of diseased cartilage **1005** in the posterior portion of the femoral condyle. **FIG. 10B** depicts placement of a single component articular surface repair system **1010**. The implantation site has been prepared with a single cut. The articular surface repair system is not perpendicular to the adjacent normal cartilage **1000**. **FIG. 10C** depicts a multi-component articular surface repair system **1020**. The implantation site has been prepared with a single cut. The deep component **1030** has a curvature similar to that of the adjacent subchondral bone **1035**. The superficial component **1040** has a curvature similar to that of the adjacent cartilage **1000**.

FIG. 11A and **B** show exemplary single and multiple component devices. **FIG 11A** shows an exemplary a single component articular surface repair system **1100** with varying curvature and radii. In this case, the articular surface repair system is chosen to include convex and concave portions. Such devices can be preferable in a lateral femoral condyle or small joints such as the elbow joint. **FIG. 11B** depicts a multi-component articular surface repair system with a deep component **1110** that mirrors the shape of the subchondral bone and a superficial component **1105** closely matching the shape and curvature of the surrounding normal cartilage **1115**. The deep component **1110** and the superficial component **1105** demonstrate varying curvatures and radii with convex and concave portions.

Detailed Description of the Invention

The current invention provides for methods and devices for integration of cartilage replacement or regenerating materials.

Before describing the present invention in detail, it is to be understood that this invention is not limited to particular formulations or process parameters as such may, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments of the invention only, and is not intended to be limiting.

The practice of the present invention employs, unless otherwise indicated, conventional methods of x-ray imaging and processing, x-ray tomosynthesis, ultrasound including A-scan, B-scan and C-scan, computed tomography (CT scan), magnetic resonance imaging (MRI), optical coherence tomography, single photon emission tomography (SPECT) and positron emission tomography (PET) within the skill of the art. Such techniques are explained fully in the literature. See, e.g., X-Ray Structure Determination: A Practical Guide, 2nd Edition, editors Stout and Jensen, 1989, John Wiley & Sons, publisher; Body CT: A Practical Approach, editor Slone, 1999, McGraw-Hill publisher; X-ray Diagnosis: A Physician's Approach, editor Lam, 1998 Springer-Verlag, publisher; and Dental Radiology: Understanding the X-Ray Image, editor Laetitia Brocklebank 1997, Oxford University Press publisher.

All publications, patents and patent applications cited herein, whether above or below, are hereby incorporated by reference in their entirety.

It must be noted that, as used in this specification and the appended claims, the singular forms "a", "an", and "the" include plural references unless the content clearly dictates otherwise. Thus, for example, reference to "an implantation site" includes a one or more such sites.

Definitions

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which the invention pertains. Although any methods and materials similar or equivalent to those described herein can be used in the practice for testing of the present invention, the preferred materials and methods are described herein.

The term "arthritis" refers to a group of conditions characterized by progressive deterioration of joints. Thus, the term encompasses a group of different diseases including, but not limited to, osteoarthritis (OA), rheumatoid arthritis, seronegative spondyloarthropathies and posttraumatic joint deformity.

The term "articular" refers to any joint. Thus, "articular cartilage" refers to cartilage in a joint such as a knee, ankle, hip, etc. The term "articular surface" refers to a surface of an articulating bone that is covered by cartilage. For example, in a knee joint several different articular surfaces are present, e.g. in the patella, the medial femoral condyle, the lateral femoral condyle, the medial tibial plateau and the lateral tibial plateau.

The term "weight-bearing surface" refers to the contact area between two opposing articular surfaces during activities of normal daily living.

The term "cartilage" or "cartilage tissue" as used herein is generally recognized in the art, and refers to a specialized type of dense connective tissue comprising cells embedded in an extracellular matrix (ECM) (see, for example, Cormack, 1987, Ham's Histology, 9th Ed., J. B. Lippincott Co., pp. 266-272). The biochemical composition of cartilage differs according to type Several types of cartilage are recognized in the art, including, for example, hyaline cartilage such as that found within the joints, fibrous cartilage such as that found within the meniscus and costal regions, and elastic cartilage. Hyaline cartilage, for example, comprises chondrocytes surrounded by a dense ECM consisting of collagen, proteoglycans and water. Fibrocartilage can form in areas of hyaline cartilage, for example after an injury or, more typically, after certain types of surgery. The production of any type of cartilage is intended to fall within the scope of the invention.

Furthermore, although described primarily in relation to methods for use in humans, the invention may also be practiced so as repair cartilage tissue in any mammal in need thereof, including horses, dogs, cats, sheep, pigs, among others. The treatment of such animals is intended to fall within the scope of the invention.

The terms "articular repair system" and "articular surface repair system" include any system (including, for example, compositions, devices and techniques) to repair, to replace or to regenerate a portion of a joint or an entire joint. The term encompasses systems that repair articular cartilage, articular bone or both bone and

cartilage. Articular surface repair systems may also include a meniscal repair system (*e.g.*, meniscal repair system can be composed of a biologic or non-biologic material), for example a meniscal repair system having biomechanical and/or biochemical properties similar to that of healthy menisci. See, for example, U.S. Patent Publication No. US 2002/00228841A1. The meniscal repair system can be surgically or arthroscopically attached to the joint capsule or one or more ligaments. Non-limiting examples of repair systems include autologous chondrocyte transplantation, osteochondral allografting, osteochondral autografting, tibial corticotomy, femoral and/or tibial osteotomy. Repair systems also include treatment with cartilage or bone tissue grown *ex vivo*, stem cells, cartilage material grown with use of stem cells, fetal cells or immature or mature cartilage cells, an artificial non-human material, an agent that stimulates repair of diseased cartilage tissue, an agent that stimulates growth of cells, an agent that protects diseased cartilage tissue and that protects adjacent normal cartilage tissue. Articular repair systems include also treatment with a cartilage tissue transplant, a cartilage tissue graft, a cartilage tissue implant, a cartilage tissue scaffold, or any other cartilage tissue replacement or regenerating material. Articular repair systems include also surgical tools that facilitate the surgical procedure required for articular repair, for example tools that prepare the area of diseased cartilage tissue and/or subchondral bone for receiving, for example, a cartilage tissue replacement or regenerating material. The term "non-pliable" refers to material that cannot be significantly bent but may retain elasticity.

The terms "replacement material" or "regenerating material" include a broad range of natural and/or synthetic materials used in the methods described herein, for example, cartilage or bone tissue grown *ex vivo*, stem cells, cartilage material grown from stem cells, stem cells, fetal cell, immature or mature cartilage cells, an agent that stimulates growth of cells, an artificial non-human material, a cartilage tissue transplant, a cartilage tissue graft, a cartilage tissue implant, a cartilage tissue scaffold, or a cartilage tissue regenerating material. The term includes biological materials isolated from various sources (*e.g.*, cells) as well as modified (*e.g.*, genetically modified) materials and/or combinations of isolated and modified materials.

The term "imaging test" includes, but is not limited to, x-ray based techniques (such as conventional film based x-ray films, digital x-ray images, single and dual x-

ray absorptiometry, radiographic absorptiometry); digital x-ray tomosynthesis, x-ray imaging including digital x-ray tomosynthesis with use of x-ray contrast agents, for example after intra-articular injection, ultrasound including broadband ultrasound attenuation measurement and speed of sound measurements, A-scan, B-scan and C-scan; computed tomography; nuclear scintigraphy; SPECT; positron emission tomography, optical coherence tomography and MRI. One or more of these imaging tests may be used in the methods described herein, for example in order to obtain certain morphological information about one or several tissues such as bone including bone mineral density and curvature of the subchondral bone, cartilage including biochemical composition of cartilage, cartilage thickness, cartilage volume, cartilage curvature, size of an area of diseased cartilage, severity of cartilage disease or cartilage loss, marrow including marrow composition, synovium including synovial inflammation, lean and fatty tissue, and thickness, dimensions and volume of soft and hard tissues. The imaging test can be performed with use of a contrast agent, such as Gd-DTPA in the case of MRI.

The term *"A – scan"* refers to an ultrasonic technique where an ultrasonic source transmits an ultrasonic wave into an object, such as patient's body, and the amplitude of the returning echoes (signals) are recorded as a function of time. Only structures that lie along the direction of propagation are interrogated. As echoes return from interfaces within the object or tissue, the transducer crystal produces a voltage that is proportional to the echo intensity. The sequence of signal acquisition and processing of the A - scan data in a modern ultrasonic instrument usually occurs in six major steps:

(1) *Detection* of the echo (signal) occurs via mechanical deformation of the piezoelectric crystal and is converted to an electric signal having a small voltage.

(2) *Preamplification* of the electronic signal from the crystal, into a more useful range of voltages is usually necessary to ensure appropriate signal processing.

(3) *Time Gain Compensation* compensates for the attenuation of the ultrasonic signal with time, which arises from travel distance. Time gain compensation may be user-adjustable and may be changed to meet the needs

of the specific application. Usually, the ideal time gain compensation curve corrects the signal for the depth of the reflective boundary. Time gain compensation works by increasing the amplification factor of the signal as a function of time after the ultrasonic pulse has been emitted. Thus, reflective boundaries having equal abilities to reflect ultrasonic waves will have equal ultrasonic signals, regardless of the depth of the boundary.

(4) *Compression* of the time compensated signal can be accomplished using logarithmic amplification to reduce the large dynamic range (range of smallest to largest signals) of the echo amplitudes. Small signals are made larger and large signals are made smaller. This step provides a convenient scale for display of the amplitude variations on the limited gray scale range of a monitor.

(5) *Rectification, demodulation and envelope detection* of the high frequency electronic signal permits the sampling and digitization of the echo amplitude free of variations induced by the sinusoidal nature of the waveform.

(6) *Rejection* level adjustment sets the threshold of signal amplitudes that are permitted to enter a data storage, processing or display system. Rejection of lower signal amplitudes reduces noise levels from scattered ultrasonic signals.

The term "*B – scan*" refers to an ultrasonic technique where the amplitude of the detected returning echo is recorded as a function of the transmission time, the relative location of the detector in the probe and the signal amplitude. This is often represented by the brightness of a visual element, such as a pixel, in a two-dimensional image. The position of the pixel along the y-axis represents the depth, i.e. half the time for the echo to return to the transducer (for one half of the distance traveled). The position along the x-axis represents the location of the returning echoes relative to the long axis of the transducer, i.e. the location of the pixel either in a superoinferior or mediolateral direction or a combination of both. The display of multiple adjacent scan lines creates a composite two-dimensional image that portrays the general contour of internal organs.

The term "*C - scan*" refers to an ultrasonic technique where additional gating electronics are incorporated into a B-scan to eliminate interference from underlying or overlying structures by scanning at a constant-depth. An interface reflects part of the

ultrasonic beam energy. All interfaces along the scan line may contribute to the measurement. The gating electronics of the C - mode rejects all returning echoes except those received during a specified time interval. Thus, only scan data obtained from a specific depth range are recorded. Induced signals outside the allowed period are not amplified and, thus, are not processed and displayed. C-mode-like methods are also described herein for A-scan techniques and devices in order to reduce the probe/skin interface reflection.The term "repair" is used in a broad sense to refer to one or more repairs to damaged joints (*e.g.*, cartilage or bone) or to replacement of one or more components or regions of the joint. Thus, the term encompasses both repair (*e.g.*, one or more portions of a cartilage and/or layers of cartilage or bone) and replacement (*e.g.*, of an entire cartilage).

General Overview

The present invention provides methods and compositions for repairing joints, particularly for repairing articular cartilage and for facilitating the integration of a wide variety of cartilage repair materials into a subject. Among other things, the techniques described herein allow for the customization of cartilage repair material to suit a particular subject, for example in terms of size, cartilage thickness and/or curvature. When the shape (*e.g.*, size, thickness and/or curvature) of the articular cartilage surface is an exact or near anatomic fit with the non-damaged cartilage or with the subject's original cartilage, the success of repair is enhanced. The repair material may be shaped prior to implantation and such shaping can be based, for example, on electronic images that provide information regarding curvature or thickness of any "normal" cartilage surrounding the defect and/or on curvature of the bone underlying the defect. Thus, the current invention provides, among other things, for minimally invasive methods for partial joint replacement. The methods will require only minimal or, in some instances, no loss in bone stock. Additionally, unlike with current techniques, the methods described herein will help to restore the integrity of the articular surface by achieving an exact or near anatomic match between the implant and the surrounding or adjacent cartilage and/or subchondral bone.

Advantages of the present invention can include, but are not limited to, (i) customization of joint repair, thereby enhancing the efficacy and comfort level for the patient following the repair procedure; (ii) eliminating the need for a surgeon to measure the defect to be repaired intraoperatively in some embodiments; (iii) eliminating the need for a surgeon to shape the material during the implantation procedure; (iv) providing methods of evaluating curvature of the repair material based on bone or tissue images or based on intraoperative probing techniques; (v) providing methods of repairing joints with only minimal or, in some instances, no loss in bone stock; and (vi) improving postoperative joint congruity.

Thus, the methods described herein allow for the design and use of joint repair material that more precisely fits the defect (*e.g.*, site of implantation) and, accordingly, provides improved repair of the joint.

1.0. Assessment of Defects

The methods and compositions described herein may be used to treat defects resulting from disease of the cartilage (e.g., osteoarthritis), bone damage, cartilage damage, trauma, and/or degeneration due to overuse or age. The invention allows, among other things, a health practitioner to evaluate and treat such defects. The size, volume and shape of the area of interest may include only the region of cartilage that has the defect, but preferably will also include contiguous parts of the cartilage surrounding the cartilage defect.

Size, curvature and/or thickness measurements can be obtained using any suitable techniques, for example in one direction, two directions, and/or in three dimensions for example, using suitable mechanical means, laser devices, molds, materials applied to the articular surface that harden and "memorize the surface contour," and/or one or more imaging techniques. Measurements may be obtained non-invasively and/or intraoperatively (*e.g.*, using a probe or other surgical device).

1.1. Imaging Techniques

Non-limiting examples of imaging techniques suitable for measuring thickness and/or curvature (*e.g.*, of cartilage and/or bone) or size of areas of diseased cartilage or cartilage loss include the use of x-rays, magnetic resonance imaging (MRI),

computed tomography scanning (CT, also known as computerized axial tomography or CAT), optical coherence tomography, SPECT, PET, ultrasound imaging techniques, and optical imaging techniques. (See, also, International Patent Publication WO 02/22014; U.S. Patent No. 6,373,250 and Vandeberg et al. (2002) *Radiology* 222:430-436).

In certain embodiments, CT or MRI is used to assess tissue, bone, cartilage and any defects therein, for example cartilage lesions or areas of diseased cartilage, to obtain information on subchondral bone or cartilage degeneration and to provide morphologic or biochemical or biomechanical information about the area of damage. Specifically, changes such as fissuring, partial or full thickness cartilage loss, and signal changes within residual cartilage can be detected using one or more of these methods. For discussions of the basic NMR principles and techniques, see MRI Basic Principles and Applications, Second Edition, Mark A. Brown and Richard C. Semelka, Wiley-Liss, Inc. (1999). For a discussion of MRI including conventional T1 and T2-weighted spin-echo imaging, gradient recalled echo (GRE) imaging, magnetization transfer contrast (MTC) imaging, fast spin-echo (FSE) imaging, contrast enhanced imaging, rapid acquisition relaxation enhancement, (RARE) imaging, gradient echo acquisition in the steady state, (GRASS), and driven equilibrium Fourier transform (DEFT) imaging, to obtain information on cartilage, see WO 02/22014. Thus, in preferred embodiments, the measurements are three-dimensional images obtained as described in WO 02/22014. Three-dimensional internal images, or maps, of the cartilage alone or in combination with a movement pattern of the joint can be obtained. Three-dimensional internal images can include information on biochemical composition of the articular cartilage. In addition, imaging techniques can be compared over time, for example to provide up to date information on the size and type of repair material needed.

Any of the imaging devices described herein may also be used intra-operatively (see, also below), for example using a hand-held ultrasound and/or optical probe to image the articular surface intra-operatively.

1.2. Intra-operative Measurements

Alternatively, or in addition to, non-invasive imaging techniques, measurements of the size of an area of diseased cartilage or an area of cartilage loss, measurements of cartilage thickness and/or curvature of cartilage or bone can be obtained intraoperatively during arthroscopy or open arthrotomy. Intraoperative measurements may or may not involve actual contact with one or more areas of the articular surfaces.

Devices to obtain intraoperative measurements of cartilage, and to generate a topographical map of the surface include but are not limited to, Placido disks and laser interferometers, and/or deformable materials. (See, for example, U.S. Patent Numbers 6,382,028; 6,057,927; 5,523,843; 5,847,804; and 5,684,562). For example, a Placido disk (a concentric array that projects well-defined circles of light of varying radii, generated either with laser or white light transported via optical fiber) can be attached to the end of an endoscopic device (or to any probe, for example a hand-held probe) so that the circles of light are projected onto the cartilage surface. One or more imaging cameras can be used (*e.g.*, attached to the device) to capture the reflection of the circles. Mathematical analysis is used to determine the surface curvature. The curvature can then be visualized on a monitor as a color-coded, topographical map of the cartilage surface. Additionally, a mathematical model of the topographical map can be used to determine the ideal surface topography to replace any cartilage defects in the area analyzed. This computed, ideal surface can then also be visualized on the monitor, and is used to select the curvature of the replacement material or regenerating material.

Similarly a laser interferometer can also be attached to the end of an endoscopic device. In addition, a small sensor may be attached to the device in order to determine the cartilage surface curvature using phase shift interferometry, producing a fringe pattern analysis phase map (wave front) visualization of the cartilage surface. The curvature can then be visualized on a monitor as a color coded, topographical map of the cartilage surface. Additionally, a mathematical model of the topographical map can be used to determine the ideal surface topography to replace any cartilage defects in the area analyzed. This computed, ideal surface can then also

visualized on the monitor, and can be used to select the curvature of the replacement cartilage.

One skilled in the art will readily recognize other techniques for optical measurements of the cartilage surface curvature.

Mechanical devices (*e.g.*, probes) may also be used for intraoperative measurements, for example, deformable materials such as gels, molds, any hardening materials (*e.g.*, materials that remain deformable until they are heated, cooled, or otherwise manipulated). See, *e.g.*, WO 02/34310. For example, a deformable gel can be applied to a femoral condyle. The side of the gel pointing towards the condyle will yield a negative impression of the surface contour of the condyle. Said negative impression can be used to determine the size of a defect, the depth of a defect and the curvature of the articular surface in and adjacent to a defect. This information can be used to select a therapy, e.g. an articular surface repair system. In another example, a hardening material can be applied to an articular surface, e.g. a femoral condyle or a tibial plateau. Said hardening material will remain on the articular surface until hardening has occurred. The hardening material will then be removed from the articular surface. The side of the hardening material pointing towards the articular surface will yield a negative impression of the articular surface. The negative impression can be used to determine the size of a defect, the depth of a defect and the curvature of the articular surface in and adjacent to a defect. This information can be used to select a therapy, e.g. an articular surface repair system.

In certain embodiments, the deformable material comprises a plurality of individually moveable mechanical elements. When pressed against the surface of interest, each element may be pushed in the opposing direction and the extent to which it is pushed (deformed) will correspond to the curvature of the surface of interest. The device may include a brake mechanism so that the elements are maintained in the position that mirrors the surface of the cartilage and/or bone. The device can then be removed from the patient and analyzed for curvature. Alternatively, each individual moveable element may include markers indicating the amount and/or degree they are deformed at a given spot. A camera can be used to intra-operatively image the device and the image can be saved and analyzed for curvature information. Suitable markers include, but are not limited to, actual linear

measurements (metric or imperial), different colors corresponding to different amounts of deformation and/or different shades or hues of the same color(s).

Other devices to measure cartilage and subchondral bone intraoperatively include, for example, ultrasound probes. An ultrasound probe, preferably handheld, can be applied to the cartilage and the curvature of the cartilage and/or the subchondral bone can be measured. Moreover, the size of a cartilage defect can be assessed and the thickness of the articular cartilage can be determined. Such ultrasound measurements can be obtained in A-mode, B-mode, or C-mode. If A-mode measurements are obtained, an operator will typically repeat the measurements with several different probe orientations, e.g. mediolateral and anteroposterior, in order to derive a three-dimensional assessment of size, curvature and thickness.

One skilled in the art will easily recognize that different probe designs are possible using said optical, laser interferometry, mechanical and ultrasound probes. The probes are preferably handheld. In certain embodiments, the probes or at least a portion of the probe, typically the portion that is in contact with the tissue, will be sterile. Sterility can be achieved with use of sterile covers, for example similar to those disclosed in WO9908598A1.

Analysis on the curvature of the articular cartilage or subchondral bone using imaging tests and/or intraoperative measurements can be used to determine the size of an area of diseased cartilage or cartilage loss. For example, the curvature can change abruptly in areas of cartilage loss. Such abrupt or sudden changes in curvature can be used to detect the boundaries of diseased cartilage or cartilage defects.

1.3. Models

Using information on thickness and curvature of the cartilage, a physical model of the surfaces of the articular cartilage and of the underlying bone can be created. This physical model can be representative of a limited area within the joint or it can encompass the entire joint. For example, in the knee joint, the physical model can encompass only the medial or lateral femoral condyle, both femoral condyles and the notch region, the medial tibial plateau, the lateral tibial plateau, the entire tibial plateau, the medial patella, the lateral patella, the entire patella or the entire joint. The location of a diseased area of cartilage can be determined, for example using a 3D

coordinate system or a 3D Euclidian distance as described in WO 02/22014.

In this way, the size of the defect to be repaired can be determined. As will be apparent, some, but not all, defects will include less than the entire cartilage. Thus, in one embodiment of the invention, the thickness of the normal or only mildly diseased cartilage surrounding one or more cartilage defects is measured. This thickness measurement can be obtained at a single point or, preferably, at multiple points, for example 2 point, 4-6 points, 7-10 points, more than 10 points or over the length of the entire remaining cartilage. Furthermore, once the size of the defect is determined, an appropriate therapy (*e.g.*, articular repair system) can be selected such that as much as possible of the healthy, surrounding tissue is preserved.

In other embodiments, the curvature of the articular surface can be measured to design and/or shape the repair material. Further, both the thickness of the remaining cartilage and the curvature of the articular surface can be measured to design and/or shape the repair material. Alternatively, the curvature of the subchondral bone can be measured and the resultant measurement(s) can be used to either select or shape a cartilage replacement material.

2.0. Repair Materials

A wide variety of materials find use in the practice of the present invention, including, but not limited to, plastics, metals, ceramics, biological materials (*e.g.*, collagen or other extracellular matrix materials), hydroxyapatite, cells (*e.g.*, stem cells, chondrocyte cells or the like), or combinations thereof. Based on the information (*e.g.*, measurements) obtained regarding the defect and the articular surface and/or the subchondral bone, a repair material can be formed or selected. Further, using one or more of these techniques described herein, a cartilage replacement or regenerating material having a curvature that will fit into a particular cartilage defect, will follow the contour and shape of the articular surface, and will match the thickness of the surrounding cartilage can be made. The repair material may include any combination of materials, and preferably includes at least one non-pliable (hard) material.

2.1. Metal and Polymeric Repair Materials

Currently, joint repair systems often employ metal and/or polymeric materials including, for example, prosthesis which are anchored into the underlying bone (*e.g.*, a femur in the case of a knee prosthesis). See, *e.g.*, U.S. Patent No. 6,203,576 and 6,322,588 and references cited therein. A wide-variety of metals may find use in the practice of the present invention, and may be selected based on any criteria, for example, based on resiliency to impart a desired degree of rigidity. Non-limiting examples of suitable metals include silver, gold, platinum, palladium, iridium, copper, tin, lead, antimony, bismuth, zinc, titanium, cobalt, stainless steel, nickel, iron alloys, cobalt alloys, such as Elgiloy®, a cobalt-chromium-nickel alloy, and MP35N, a nickel-cobalt-chromium-molybdenum alloy, and Nitinol™, a nickel-titanium alloy, aluminum, manganese, iron, tantalum, other metals that can slowly form polyvalent metal ions, for example to inhibit calcification of implanted substrates in contact with a patient's bodily fluids or tissues, and combinations thereof.

Suitable synthetic polymers include, without limitation, polyamides (e.g., nylon), polyesters, polystyrenes, polyacrylates, vinyl polymers (e.g., polyethylene, polytetrafluoroethylene, polypropylene and polyvinyl chloride), polycarbonates, polyurethanes, poly dimethyl siloxanes, cellulose acetates, polymethyl methacrylates, polyether ether ketones, ethylene vinyl acetates, polysulfones, nitrocelluloses, similar copolymers and mixtures thereof. Bioresorbable synthetic polymers can also be used such as dextran, hydroxyethyl starch, derivatives of gelatin, polyvinylpyrrolidone, polyvinyl alcohol, poly[N-(2-hydroxypropyl) methacrylamide], poly(hydroxy acids), poly(epsilon-caprolactone), polylactic acid, polyglycolic acid, poly(dimethyl glycolic acid), poly(hydroxy butyrate), and similar copolymers may also be used.

The polymers can be prepared by any of a variety of approaches including conventional polymer processing methods. Preferred approaches include, for example, injection molding, which is suitable for the production of polymer components with significant structural features, and rapid prototyping approaches, such as reaction injection molding and stereo-lithography. The substrate can be textured or made porous by either physical abrasion or chemical alteration to facilitate incorporation of the metal coating.

More than one metal and/or polymer may be used in combination with each other. For example, one or more metal-containing substrates may be coated with polymers in one or more regions or, alternatively, one or more polymer-containing substrate may be coated in one or more regions with one or more metals.

The device can be porous or porous coated. The porous surface components can be made of various materials including metals, ceramics, and polymers. These surface components can, in turn, be secured by various means to a multitude of structural cores formed of various metals. Suitable porous coatings include, but are not limited to, metal, ceramic, polymeric (*e.g.*, biologically neutral elastomers such as silicone rubber, polyethylene terephthalate and/or combinations thereof) or combinations thereof. *See, e.g.*, Hahn U.S. Pat. No. 3,605,123. Tronzo U.S. Pat. No. 3,808,606 and Tronzo U.S. Pat. No. 3,843,975; Smith U.S. Pat. No. 3,314,420; Scharbach U.S. Pat. No. 3,987,499; and German Offenlegungsschrift 2,306,552. There may be more than one coating layer and the layers may have the same or different porosities. See, *e.g.*, U.S. Pat. No. 3,938,198.

The coating may be applied by surrounding a core with powdered polymer and heating until cured to form a coating with an internal network of interconnected pores. The tortuosity of the pores (*e.g.*, a measure of length to diameter of the paths through the pores) may be important in evaluating the probable success of such a coating in use on a prosthetic device. See, also, Morris U.S. Pat. No. 4,213,816. The porous coating may be applied in the form of a powder and the article as a whole subjected to an elevated temperature that bonds the powder to the substrate. Selection of suitable polymers and/or powder coatings may be determined in view of the teachings and references cited herein, for example based on the melt index of each.

2.2. Biological Repair Materials

Repair materials may also include one or more biological material either alone or in combination with non-biological materials. For example, any base material can be designed or shaped and suitable cartilage replacement or regenerating material(s) such as fetal cartilage cells can be applied to be the base. The cells can be then be grown in conjunction with the base until the thickness (and/or curvature) of the cartilage surrounding the cartilage defect has been reached. Conditions for growing

cells (*e.g.*, chondrocytes) on various substrates in culture, *ex vivo* and *in vivo* are described, for example, in U.S. Patent Nos. 5,478,739; 5,842,477; 6,283,980 and 6,365,405. Non-limiting examples of suitable substrates include plastic, tissue scaffold, a bone replacement material (*e.g.*, a hydroxyapatite, a bioresorbable material), or any other material suitable for growing a cartilage replacement or regenerating material on it.

Biological polymers can be naturally occurring or produced in vitro by fermentation and the like. Suitable biological polymers include, without limitation, collagen, elastin, silk, keratin, gelatin, polyamino acids, cat gut sutures, polysaccharides (e.g., cellulose and starch) and mixtures thereof. Biological polymers may be bioresorbable.

Biological materials used in the methods described herein can be autografts (from the same subject); allografts (from another individual of the same species) and/or xenografts (from another species). See, also, International Patent Publications WO 02/22014 and WO 97/27885. In certain embodiments autologous materials are preferred, as they may carry a reduced risk of immunological complications to the host, including re-absorption of the materials, inflammation and/or scarring of the tissues surrounding the implant site.

In one embodiment of the invention, a probe is used to harvest tissue from a donor site and to prepare a recipient site. The donor site can be located in a xenograft, an allograft or an autograft. The probe is used to achieve a good anatomic match between the donor tissue sample and the recipient site. The probe is specifically designed to achieve a seamless or near seamless match between the donor tissue sample and the recipient site. The probe can, for example, be cylindrical. The distal end of the probe is typically sharp in order to facilitate tissue penetration. Additionally, the distal end of the probe is typically hollow in order to accept the tissue. The probe can have an edge at a defined distance from its distal end, e.g. at 1 cm distance from the distal end and the edge can be used to achieve a defined depth of tissue penetration for harvesting. The edge can be external or can be inside the hollow portion of the probe. For example, an orthopedic surgeon can take the probe and advance it with physical pressure into the cartilage, the subchondral bone and the underlying marrow in the case of a joint such as a knee joint. The surgeon can

advance the probe until the external or internal edge reaches the cartilage surface. At that point, the edge will prevent further tissue penetration thereby achieving a constant and reproducible tissue penetration. The distal end of the probe can include a blade or saw-like structure or tissue cutting mechanism. For example, the distal end of the probe can include an iris-like mechanism consisting of several small blades. The at least one or more blades can be moved using a manual, motorized or electrical mechanism thereby cutting through the tissue and separating the tissue sample from the underlying tissue. Typically, this will be repeated in the donor and the recipient. In the case of an iris-shaped blade mechanism, the individual blades can be moved so as to close the iris thereby separating the tissue sample from the donor site.

In another embodiment of the invention, a laser device or a radiofrequency device can be integrated inside the distal end of the probe. The laser device or the radiofrequency device can be used to cut through the tissue and to separate the tissue sample from the underlying tissue.

In one embodiment of the invention, the same probe can be used in the donor and in the recipient. In another embodiment, similarly shaped probes of slightly different physical dimensions can be used. For example, the probe used in the recipient can be slightly smaller than that used in the donor thereby achieving a tight fit between the tissue sample or tissue transplant and the recipient site. The probe used in the recipient can also be slightly shorter than that used in the donor thereby correcting for any tissue lost during the separation or cutting of the tissue sample from the underlying tissue in the donor material.

Any biological repair material may be sterilized to inactivate biological contaminants such as bacteria, viruses, yeasts, molds, mycoplasmas and parasites. Sterilization may be performed using any suitable technique, for example radiation, such as gamma radiation.

Any of the biological material described herein may be harvested with use of a robotic device. The robotic device can use information from an electronic image for tissue harvesting.

In certain embodiments, the cartilage replacement material has a particular biochemical composition. For instance, the biochemical composition of the cartilage surrounding a defect can be assessed by taking tissue samples and chemical analysis

or by imaging techniques. For example, WO 02/22014 describes the use of gadolinium for imaging of articular cartilage to monitor glycosaminoglycan content within the cartilage. The cartilage replacement or regenerating material can then be made or cultured in a manner, to achieve a biochemical composition similar to that of the cartilage surrounding the implantation site. The culture conditions used to achieve the desired biochemical compositions can include, for example, varying concentrations biochemical composition of said cartilage replacement or regenerating material can, for example, be influenced by controlling concentrations and exposure times of certain nutrients and growth factors.

2.3. Multiple-component Repair Materials

The articular surface repair system may include one or more components. Non-limiting examples of one-component systems include a plastic, a metal, a metal alloy or a biologic material. In certain embodiments, the surface of the repair system facing the underlying bone is smooth. In other embodiments, the surface of the repair system facing the underlying bone is porous or porous-coated.

Non-limiting examples of multiple-component systems include combinations of metal, plastic, metal alloys and one or more biological materials. One or more components of the articular surface repair system can be composed of a biologic material (e.g. a tissue scaffold with cells such as cartilage cells or stem cells alone or seeded within a substrate such as a bioresorable material or a tissue scaffold, allograft, autograft or combinations thereof) and/or a non-biological material (*e.g.*, polyethylene or a chromium alloy such as chromium cobalt).

Thus, the repair system can include one or more areas of a single material or a combination of materials, for example, the articular surface repair system can have a superficial and a deep component. The superficial component is typically designed to have size, thickness and curvature similar to that of the cartilage tissue lost while the deep component is typically designed to have a curvature similar to the subchondral bone. In addition, the superficial component can have biomechanical properties similar to articular cartilage, including but not limited to similar elasticity and resistance to axial loading or shear forces. The superficial and the deep component can consist of two different metals or metal alloys. One or more components of the

system (*e.g.*, the deep portion) can be composed of a biologic material including, but not limited to bone, or a non-biologic material including, but not limited to hydroxyapatite, tantalum, a chromium alloy, chromium cobalt or other metal alloys.

One or more regions of the articular surface repair system (*e.g.*, the outer margin of the superficial portion and/or the deep portion) can be bioresorbable, for example to allow the interface between the articular surface repair system and the patient's normal cartilage, over time, to be filled in with hyaline or fibrocartilage. Similarly, one or more regions (*e.g.*, the outer margin of the superficial portion of the articular surface repair system and/or the deep portion) can be porous. The degree of porosity can change throughout the porous region, linearly or non-linearly, for where the degree of porosity will typically decrease towards the center of the articular surface repair system. The pores can be designed for in-growth of cartilage cells, cartilage matrix, and connective tissue thereby achieving a smooth interface between the articular surface repair system and the surrounding cartilage.

The repair system (*e.g.*, the deep component in multiple component systems) can be attached to the patient's bone with use of a cement-like material such as methylmethacrylate, injectable hydroxy- or calcium-apatite materials and the like.

In certain embodiments, one or more portions of the articular surface repair system can be pliable or liquid or deformable at the time of implantation and can harden later. Hardening can occur within 1 second to 2 hours (or any time period therebetween), preferably with in 1 second to 30 minutes (or any time period therebetween), more preferably between 1 second and 10 minutes (or any time period therebetween).

One or more components of the articular surface repair system can be adapted to receive injections. For example, the external surface of the articular surface repair system can have one or more openings therein. The openings can be sized so as to receive screws, tubing, needles or other devices which can be inserted and advanced to the desired depth, for example through the articular surface repair system into the marrow space. Injectables such as methylmethacrylate and injectable hydroxy- or calcium-apatite materials can then be introduced through the opening (or tubing inserted therethrough) into the marrow space thereby bonding the articular surface repair system with the marrow space. Similarly, screws or pins can be inserted into

the openings and advanced to the underlying subchondral bone and the bone marrow or epiphysis to achieve fixation of the articular surface repair system to the bone. Portions or all components of the screw or pin can be bioresorbable, for example, the distal portion of a screw that protrudes into the marrow space can be bioresorbable. During the initial period after the surgery, the screw can provide the primary fixation of the articular surface repair system. Subsequently, ingrowth of bone into a porous coated area along the undersurface of the articular cartilage repair system can take over as the primary stabilizer of the articular surface repair system against the bone.

The articular surface repair system can be anchored to the patient's bone with use of a pin or screw or other attachment mechanism. The attachment mechanism can be bioresorbable. The screw or pin or attachment mechanism can be inserted and advanced towards the articular surface repair system from a non-cartilage covered portion of the bone or from a non-weight-bearing surface of the joint.

The interface between the articular surface repair system and the surrounding normal cartilage can be at an angle, for example oriented at an angle of 90 degrees relative to the underlying subchondral bone. Suitable angles can be determined in view of the teachings herein, and in certain cases, non-90 degree angles may have advantages with regard to load distribution along the interface between the articular surface repair system and the surrounding normal cartilage.

The interface between the articular surface repair system and the surrounding normal cartilage may be covered with a pharmaceutical or bioactive agent, for example a material that stimulates the biological integration of the repair system into the normal cartilage. The surface area of the interface can be irregular, for example, to increase exposure of the interface to pharmaceutical or bioactive agents.

2.4. Customized Containers

In another embodiment of the invention, a container or well can be formed to the selected specifications, for example to match the material needed for a particular subject or to create a stock of repair materials in a variety of sizes. The size and shape of the contained may be designed using the thickness and curvature information obtained from the joint and from the cartilage defect. More specifically, the inside of the container can be shaped to follow any selected measurements, for example as

obtained from the cartilage defect(s) of a particular subject. The container can be filled with a cartilage replacement or regenerating material, for example, collagen-containing materials, plastics, bioresorbable materials and/or any suitable tissue scaffold. The cartilage regenerating or replacement material can also consist of a suspension of stem cells or fetal or immature or mature cartilage cells that subsequently develop to more mature cartilage inside the container. Further, development and/or differentiation can be enhanced with use of certain tissue nutrients and growth factors.

The material is allowed to harden and/or grow inside the container until the material has the desired traits, for example, thickness, elasticity, hardness, biochemical composition, etc. Molds can be generated using any suitable technique, for example computer devices and automation, e.g. computer assisted design (CAD) and, for example, computer assisted modeling (CAM). Because the resulting material generally follows the contour of the inside of the container it will better fit the defect itself and facilitate integration.

2.5. Shaping

In certain instances shaping of the repair material will be required before or after formation (*e.g.*, growth to desired thickness), for example where the thickness of the required cartilage material is not uniform (*e.g.*, where different sections of the cartilage replacement or regenerating material require different thicknesses).

The replacement material can be shaped by any suitable technique including, but not limited to, mechanical abrasion, laser abrasion or ablation, radiofrequency treatment, cryoablation, variations in exposure time and concentration of nutrients, enzymes or growth factors and any other means suitable for influencing or changing cartilage thickness. See, e.g., WO 00/15153; If enzymatic digestion is used, certain sections of the cartilage replacement or regenerating material can be exposed to higher doses of the enzyme or can be exposed longer as a means of achieving different thicknesses and curvatures of the cartilage replacement or regenerating material in different sections of said material.

The material can be shaped manually and/or automatically, for example using a device into which a pre-selected thickness and/or curvature has been inputted and programming the device to achieve the desired shape.

In addition to, or instead of, shaping the cartilage repair material, the site of implantation (*e.g.*, bone surface, any cartilage material remaining, etc.) can also be shaped by any suitable technique in order to enhanced integration of the repair material.

2.6. Pre-existing Repair Systems

As described herein, repair systems of various sizes, curvatures and thicknesses can be obtained. These repair systems can be catalogued and stored to create a library of systems from which an appropriate system can then be selected. In other words, a defect is assessed in a particular subject and a pre-existing repair system having the closest shape and size is selected from the library for further manipulation (*e.g.*, shaping) and implantation.

2.7. Mini-Prosthesis

As noted above, the methods and compositions described herein can be used to replace only a portion of the articular surface, for example, an area of diseased cartilage or lost cartilage on the articular surface. In these systems, the articular surface repair system may be designed to replace only the area of diseased or lost cartilage or it can extend beyond the area of diseased or lost cartilage, *e.g.*, 3 or 5 mm into normal adjacent cartilage. In certain embodiments, the prosthesis replaces less than about 70% to 80% (or any value therebetween) of the articular surface (*e.g.*, any given articular surface such as a single femoral condyle, etc.), preferably, less than about 50% to 70% (or any value therebetween), more preferably, less than about 30% to 50% (or any value therebetween), more preferably less than about 20% to 30% (or any value therebetween), even more preferably less than about 20% of the articular surface.

As noted above, the prosthesis may include multiple components, for example a component that is implanted into the bone (*e.g.*, a metallic device) attached to a component that is shaped to cover the defect of the cartilage overlaying the bone.

Additional components, for example intermediate plates, meniscus repairs systems and the like may also be included. It is contemplated that each component replaces less than all of the corresponding articular surface. However, each component need not replace the same portion of the articular surface. In other words, the prosthesis may have a bone-implanted component that replaces less than 30% of the bone and a cartilage component that replaces 60% of the cartilage. The prosthesis may include any combination, so long as each component replaces less than the entire articular surface.

The articular surface repair system may be formed or selected so that it will achieve a near anatomic fit or match with the surrounding or adjacent cartilage. Typically, the articular surface repair system is formed and/or selected so that its outer margin located at the external surface will be aligned with the surrounding or adjacent cartilage.

Thus, the articular surface repair system can be designed to replace only the weight-bearing portion of an articular surface, for example in a femoral condyle. The weight-bearing surface refers to the contact area between two opposing articular surfaces during activities of normal daily living. At least one or more weight-bearing portions can be replaced in this manner, *e.g.,* on a femoral condyle and on a tibia.

In other embodiments, an area of diseased cartilage or cartilage loss can be identified in a weight-bearing area and only a portion of said weight-bearing area, specifically the portion containing said diseased cartilage or area of cartilage loss, can be replaced with an articular surface repair system.

In certain aspects, the defect to be repaired is located only on one articular surface, typically the most diseased surface. For example, in a patient with severe cartilage loss in the medial femoral condyle but less severe disease in the tibia, the articular surface repair system can only be applied to the medial femoral condyle. Preferably, in any methods described herein, the articular surface repair system is designed to achieve an exact or a near anatomic fit with the adjacent normal cartilage.

In other embodiments, more than one articular surface can be repaired.

The area(s) of repair will be typically limited to areas of diseased cartilage or cartilage loss or areas slightly greater than the area of diseased cartilage or cartilage loss within the weight-bearing surface(s).

The implant and/or the implant site can be sculpted to achieve a near anatomic alignment between the implant and the implant site. In another embodiment of the invention, an electronic image is used to measure the thickness, curvature, or shape of the articular cartilage or the subchondral bone, and/or the size of a defect, and an articular surface repair system is selected using this information. The articular surface repair system can be inserted arthroscopically. The articular surface repair system can have a single radius. More typically, however, the articular surface repair system **1100** can have varying curvatures and radii within the same plane, e.g. anteroposterior or mediolateral or superoinferior or oblique planes, or within multiple planes. In this manner, the articular surface repair system can be shaped to achieve a near anatomic alignment between the implant and the implant site. This design allows not even for different degrees of convexity or concavity, but also for concave portions within a predominantly convex shape or vice versa **1100**.

If a multiple component repair material has been selected, for example with a superficial component **1105** consisting of a polymeric material and a deep component **1110** consisting of a metal alloy, the superficial component can be designed so that its thickness and curvature will closely match that of the surrounding cartilage **1115**. Thus, the superficial component can have more than one thickness in different portions of the articular repair system. Moreover, the superficial component can have varying curvatures and radii within the same plane, e.g. anteroposterior or mediolateral or superoinferior or oblique planes, or within multiple planes. Similarly, the deep component can have varying curvatures and radii within the same plane, e.g. anteroposterior or mediolateral or superoinferior or oblique planes, or within multiple planes. Typically, the curvature of the deep component will be designed to follow that of the subchondral bone.

In another embodiment the articular surface repair system has a fixturing stem, for example, as described in the Background of US Patent No. 6,224,632. The fixturing stem can have different shapes including conical, rectangular, fin among others. The mating bone cavity is typically similarly shaped as the corresponding stem.

In another embodiment, the articular surface repair system can be attached to the underlying bone or bone marrow using bone cement. Bone cement is typically

made from an acrylic polymeric material. Typically, the bone cement is comprised of two components: a dry power component and a liquid component, which are subsequently mixed together. The dry component generally includes an acrylic polymer, such as polymethylmethacrylate (PMMA). The dry component can also contain a polymerization initiator such as benzoylperoxide, which initiates the free-radical polymerization process that occurs when the bone cement is formed. The liquid component, on the other hand, generally contains a liquid monomer such as methyl methacrylate (MMA). The liquid component can also contain an accelerator such as an amine (e.g., N,N-dimethyl-p-toluidine). A stabilizer, such as hydroquinone, can also be added to the liquid component to prevent premature polymerization of the liquid monomer. When the liquid component is mixed with the dry component, the dry component begins to dissolve or swell in the liquid monomer. The amine accelerator reacts with the initiator to form free radicals that begin to link monomer units to form polymer chains. In the next two to four minutes, the polymerization process proceeds changing the viscosity of the mixture from a syrup-like consistency (low viscosity) into a dough-like consistency (high viscosity). Ultimately, further polymerization and curing occur, causing the cement to harden and affix a prosthesis to a bone.

In certain aspects of the invention, bone cement **955** or another liquid attachment material such as injectable calciumhydroxyapatite can be injected into the marrow cavity through one or more openings **950** in the prosthesis. These openings in the prosthesis can extend from the articular surface to the undersurface of the prosthesis **960**. After injection, the openings can be closed with a polymer, silicon, metal, metal alloy or bioresorbable plug.

In another embodiment, one or more components of the articular surface repair (*e.g.,* the surface of the system that is pointing towards the underlying bone or bone marrow) can be porous or porous coated. A variety of different porous metal coatings have been proposed for enhancing fixation of a metallic prosthesis by bone tissue ingrowth. Thus, for example, U.S. Pat. No. 3,855,638 discloses a surgical prosthetic device, which may be used as a bone prosthesis, comprising a composite structure consisting of a solid metallic material substrate and a porous coating of the same solid metallic material adhered to and extending over at least a portion of the surface of the

substrate. The porous coating consists of a plurality of small discrete particles of metallic material bonded together at their points of contact with each other to define a plurality of connected interstitial pores in the coating. The size and spacing of the particles, which can be distributed in a plurality of monolayers, can be such that the average interstitial pore size is not more than about 200 microns. Additionally, the pore size distribution can be substantially uniform from the substrate-coating interface to the surface of the coating. In another embodiment, the articular surface repair system can contain one or more polymeric materials that can be loaded with and release therapeutic agents including drugs or other pharmacological treatments that can be used for drug delivery. The polymeric materials can, for example, be placed inside areas of porous coating. The polymeric materials can be used to release therapeutic drugs, e.g. bone or cartilage growth stimulating drugs. This embodiment can be combined with other embodiments, wherein portions of the articular surface repair system can be bioresorbable. For example, the superficial layer of an articular surface repair system or portions of its superficial layer can be bioresorbable. As the superficial layer gets increasingly resorbed, local release of a cartilage growth-stimulating drug can facilitate ingrowth of cartilage cells and matrix formation.

In any of the methods or compositions described herein, the articular surface repair system can be pre-manufactured with a range of sizes, curvatures and thicknesses. Alternatively, the articular surface repair system can be custom-made for an individual patient.

3. Implantation

Following one or more manipulations (*e.g.*, shaping, growth, development, etc), the cartilage replacement or regenerating material can then be implanted into the area of the defect. Implantation can be performed with the cartilage replacement or regenerating material still attached to the base material or removed from the base material. Any suitable methods and devices may be used for implantation, for example, devices as described in U.S. Patent Nos. 6,375,658; 6,358,253; 6,328,765; and International Publication WO 01/19254.

In selected cartilage defects, the implantation site can be prepared with a single cut across the articular surface (**Fig. 10**). In this case, single **1010** and multi-component **1020** prostheses can be utilized.

Further, implantation can be facilitated by using a device applied to the outer surface of the articular cartilage in order to match the alignment of the donor tissue and the recipient site. The device can be round, circular, oval, ellipsoid, curved or irregular in shape. The shape is typically selected or adjusted to match or enclose an area of diseased cartilage or an area slightly larger than the area of diseased cartilage. The inner aspect of the circle, oval, ellipse, curved or irregular shape can be open or hollow. Thus, a rounded or curved joint surface such as a femoral condyle, a femoral head or a humeral head can protrude through the opening or the hollow portion. The device can include a slit through which a blade can be introduced. Alternatively, the device can include a blade holding mechanism or the blade can be integrated in the device. A variety of materials can be employed, for example plastic (*e.g.*, disposable, re-usable and/or sterilizable) devices. In addition, translucent materials may be used, for example in order to achieve an improved match between the donor tissue and the recipient site.

The device can be used to remove an area of diseased cartilage and underlying bone or an area slightly larger than the diseased cartilage and underlying bone. In addition, the device can be used on a "donor", e.g. a cadaveric specimen to obtain implantable repair material. The device is typically positioned in the same general anatomic area in which the tissue was removed in the recipient. The shape of the device is then used to identify a donor site providing a seamless or near seamless match between the donor tissue sample and the recipient site. This is achieved by identifying the position of the device in which the articular surface in the donor, e.g. a cadaveric specimen has a seamless or near seamless contact with the inner surface when applied to the cartilage.

The device can be molded, machined or formed based on the size of the area of diseased cartilage and based on the curvature of the cartilage or the underlying subchondral bone or a combination of both. The device can then be applied to the donor, (*e.g.*, a cadaveric specimen) and the donor tissue can be obtained with use of a blade or saw or other tissue cutting device. The device can then be applied to the

recipient in the area of the diseased cartilage and the diseased cartilage and underlying bone can be removed with use of a blade or saw or other tissue cutting device whereby the size and shape of the removed tissue containing the diseased cartilage will closely resemble the size and shape of the donor tissue. The donor tissue can then be attached to the recipient site. For example, said attachment can be achieved with use of screws or pins (*e.g.*, metallic, non-metallic or bioresorable) or other fixation means including but not limited to a tissue adhesive. Attachment can be through the cartilage surface or alternatively, through the marrow space.

The implant site can be prepared with use of a robotic device. The robotic device can use information from an electronic image for preparing the recipient site.

CLAIMS

What is claimed is:

1. A method for providing articular replacement material, the method comprising the step of producing articular replacement material of selected dimensions.

2. The method of claim 1, wherein the dimensions comprise thickness and curvature.

3. The method of claim 1, wherein the dimensions comprise size and curvature.

4. The method of claim 1, wherein the dimensions comprise size, thickness and curvature.

5. The method of any of claims 1 to 4, wherein the articular replacement material replaces cartilage and wherein said material is non-pliable.

6. The method of any of claims 1 to 5, wherein the dimensions of the articular replacement material are selected following intraoperative measurements.

7. The method of claim 6, wherein said measurements are made using imaging techniques.

8. The method of claim 7, wherein said imaging techniques are selected from the group consisting of ultrasound, MRI, CT scan, x-ray imaging obtained with x-ray dye and fluoroscopic imaging.

9. The method of claim 6, wherein said measurements are made using a mechanical probe.

10. The method of claim 9, wherein said measurements are made using an ultrasound probe, a laser, an optical probe and a deformable material.

11. The method of any of claims 1 to 10, wherein said producing step comprises growing or hardening the articular replacement material.

12. The method of any of claims 1 to 11, wherein said producing step comprises shaping the articular replacement material to the selected dimensions.

13. The method of claim 12, wherein said shaping is selected from the group consisting of mechanical abrasion, laser ablation, radiofrequency ablation, cryoablation and enzymatic digestion.

14. The method of claim 12, wherein said shaping is performed manually.

15. The method of claim 12, wherein said shaping is performed by machine.

16. The method of claim 15, wherein said shaping is automated.

17. The method of any of claims 1 to 16, wherein said articular replacement material is produced postoperatively.

18. The method of any of claims 1 to 17, wherein said articular replacement material is selected from a library of pre-existing repair systems.

19. The method of any of claims 1 to 18, wherein said articular replacement material comprises synthetic materials.

20. The method of claim 19, wherein the synthetic materials comprise metals, polymers or combinations thereof.

21. The method of claim 5, wherein said cartilage replacement material comprises biological materials.

22. The method of claim 21, wherein said biological materials comprise cells.

23. The method of claim 22, wherein said cells are stem cells, fetal cells or chondrocyte cells.

24. A method of making cartilage repair material, the method comprising the steps of

(a) measuring the dimensions of the intended implantation site or the dimensions of the area surrounding the intended implantation site; and

(b) providing cartilage replacement material that conforms to the measurements obtained in step (a).

25. The method of claim 24, wherein the step (a) comprises measuring the thickness of the cartilage surrounding the intended implantation site and measuring the curvature of the cartilage surrounding the intended implantation site.

26. The method of claim 24, wherein the step (a) comprises measuring the size of the intended implantation site and measuring the curvature of the cartilage surrounding the intended implantation site.

27. The method of claim 24, wherein the step (a) comprises measuring the thickness of the cartilage surrounding the intended implantation site, measuring the size of the intended implantation site, and measuring the curvature of the cartilage surrounding the intended implantation site.

28. The method of any of claims 24 to 27, wherein step (a) comprises obtaining and analyzing an image of the cartilage.

29. The method of claim 28, wherein said image is obtained intraoperatively.

30. The method of any of claims 24 to 30, wherein step (a) comprises using a mechanical probe intraoperatively to measure the dimensions.

31. The method of claim 30, wherein the mechanical probe comprises a deformable material.

32. The method of any of claims 24 to 31, wherein step (b) comprises selecting the cartilage replacement material from a library of pre-existing repair systems.

33. The method of any of claims 24 to 31, wherein step (b) comprises growing the cartilage replacement material.

34. The method of any of claims 24 to 33, further comprising shaping the cartilage material.

35. The method of claim 34, wherein said shaping is by machine.

36. The method of claim 34, wherein said shaping is automated.

37. The method of claim 34, wherein said shaping is selected from the group consisting of mechanical abrasion, laser ablation, radiofrequency ablation, cryoablation and enzymatic digestion.

38. The method of claim 24, wherein step (b) comprises growing cartilage replacement material comprising biological substances *ex vivo*.

39. A method of repairing a cartilage in a subject, the method of comprising the step of implantating cartilage repair material prepared according to the method of any of claims 1 to 38, into the subject.

40. A method of determining the curvature of an articular surface, the method comprising the step of (a) intraoperatively measuring the curvature of the articular surface using a mechanical probe.

41. The method of claim 40, wherein the articular surface comprises cartilage.

42. The method of claim 40, wherein the articular surface comprises subchondral bone.

43. The method of any of claims 40 to 42, wherein the mechanical probe is selected from the group consisting of an ultrasound probe, a laser, an optical probe and a deformable material.

44. A method of producing an articular replacement material comprising the step of providing an articular replacement material that conforms to the measurements obtained by the methods of any of claims 40 to 43.

45. A method of repairing an articular surface in a subject, the method of comprising the step of implanting articular repair material prepared according to the method of claim 44 into the subject.

46. A partial articular prosthesis comprising

a first component comprising a cartilage replacement material; and

a second component comprising one or more metals, wherein said second component has a curvature similar to subchondral bone, wherein said prosthesis comprises less than about 80% of the articular surface.

47. The prosthesis of claim 46, wherein said first or second components comprise a non-pliable material.

48. The prosthesis of claim 46 or claim 47, wherein said first or second components further comprises a polymeric material.

49. The prosthesis of any of claims 46 to 48, wherein said first component comprises biological materials.

50. The prosthesis of any of claims 46 to 49, wherein said first component exhibits biomechanical properties similar to articular cartilage.

51. The prosthesis of claim 50, wherein said biomechanical properties are elasticity, resistance to axial loading or shear forces.

52. The prosthesis of any of claims 46 to 51, wherein the first and second components comprise two or more metals.

53. The prosthesis of any of claims 46 to 52, wherein the first or second components are bioresorbable.

54. The prosthesis of any of claims 46 to 53, wherein the first or second components are porous or porous coated.

55. The prosthesis of any of claims 46 to 53, wherein the first or second components are smooth.

56. The prosthesis of any of claims 46 to 55, wherein the first or second components are adapted to receive injections.

57. A partial articular prosthesis for use in a human with cartilage disease comprising

an external surface located in the load bearing area of an articular surface, wherein the dimensions of said external surface achieve a near anatomic fit with the adjacent cartilage.

58. The prosthesis of claim 57, further comprising one or more metals or metal alloys.

59. An articular surface repair system comprising

(a) cartilage replacement material, wherein said cartilage replacement material has a curvature similar to surrounding or adjacent cartilage; and

(b) at least one non-biologic material, wherein said articular surface repair system comprises a portion of the articular surface equal to or smaller than the weight-bearing surface.

60. The articular surface repair system of claim 59, wherein said cartilage replacement material is non-pliable.

61. The articular surface repair system of claim 59 or claim 60, wherein said cartilage replacement material has biomechanical properties similar to that of normal human cartilage.

62. The articular surface repair system of any of claims 59 to 61, wherein said cartilage replacement material has a biochemical composition similar to that of normal human cartilage.

63. An articular surface repair system comprising

a first component comprising a cartilage replacement material, wherein said first component has dimensions similar to that of adjacent or surrounding cartilage; and

a second component, wherein said second component has a curvature similar to subchondral bone, wherein said articular surface repair system comprises less than about 80% of the articular surface.

64. The repair system of claim 63, wherein said first or said second component comprises a non-pliable material.

65. The articular surface repair system of claim 63 or claim 64, wherein the first component has a curvature and thickness similar to that of adjacent or surrounding cartilage.

66. The articular surface repair system of any of claims 63 to 65, wherein said thickness of said first component is not uniform.

67. A partial articular prosthesis comprising

(a) a metal or metal alloy; and

(b) an external surface located in the load bearing area of an articular surface, wherein the external surface designed to achieve a near anatomic fit with the adjacent cartilage.

68. The partial articular prosthesis of claim 67, wherein said external surface is comprises a polymeric material attached to said metal or metal alloy.

69. An articular surface repair system comprising a cartilage replacement material, wherein said cartilage replacement material has a curvature similar to surrounding or adjacent cartilage, wherein said articular surface repair system is adapted to receive injections.

70. The articular surface repair system of claim 69, wherein said injections are made through an opening in the external surface of said cartilage replacement material.

71. The articular surface repair system of claims 69 or claim 70, wherein said opening in the external surface terminates in a plurality of openings on the bone surface.

72. The articular surface repair system of any of claims 69 to 72, wherein bone cement is injected through said opening.

73. The articular surface repair system of claim 72, wherein said bone cement is injected under pressure in order to achieve permeation of portions of the marrow space with bone cement.

74. The articular surface repair system of claim 72, wherein said bone cement is combined with a therapeutic drug.

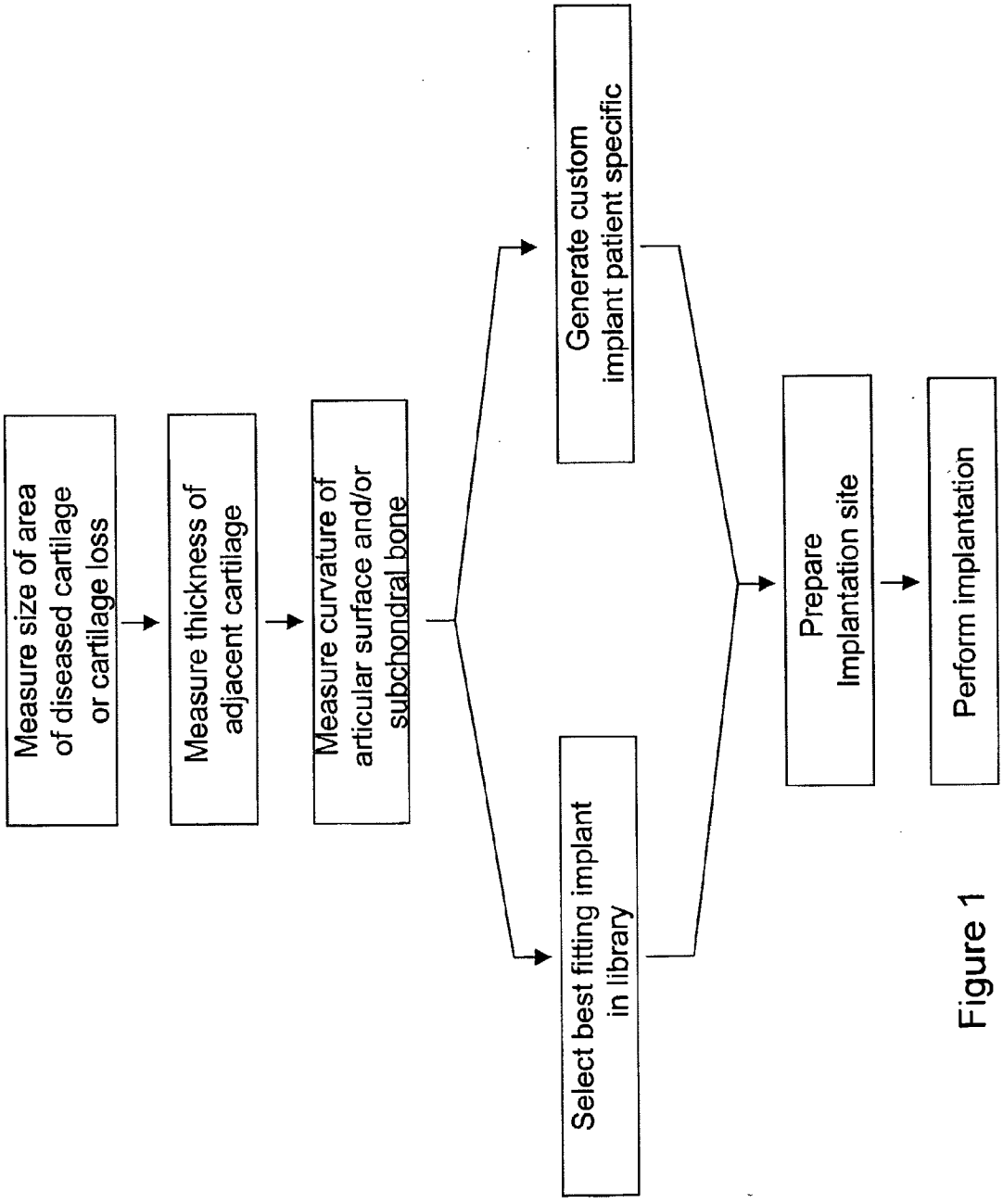

Measure size of area of diseased cartilage or cartilage loss
Measure thickness of adjacent cartilage
Measure curvature of articular surface and/or subchondral bone
Generate custom implant patient specific
Select best fitting implant in library
Prepare Implantation site
Perform implantation

Figure 1

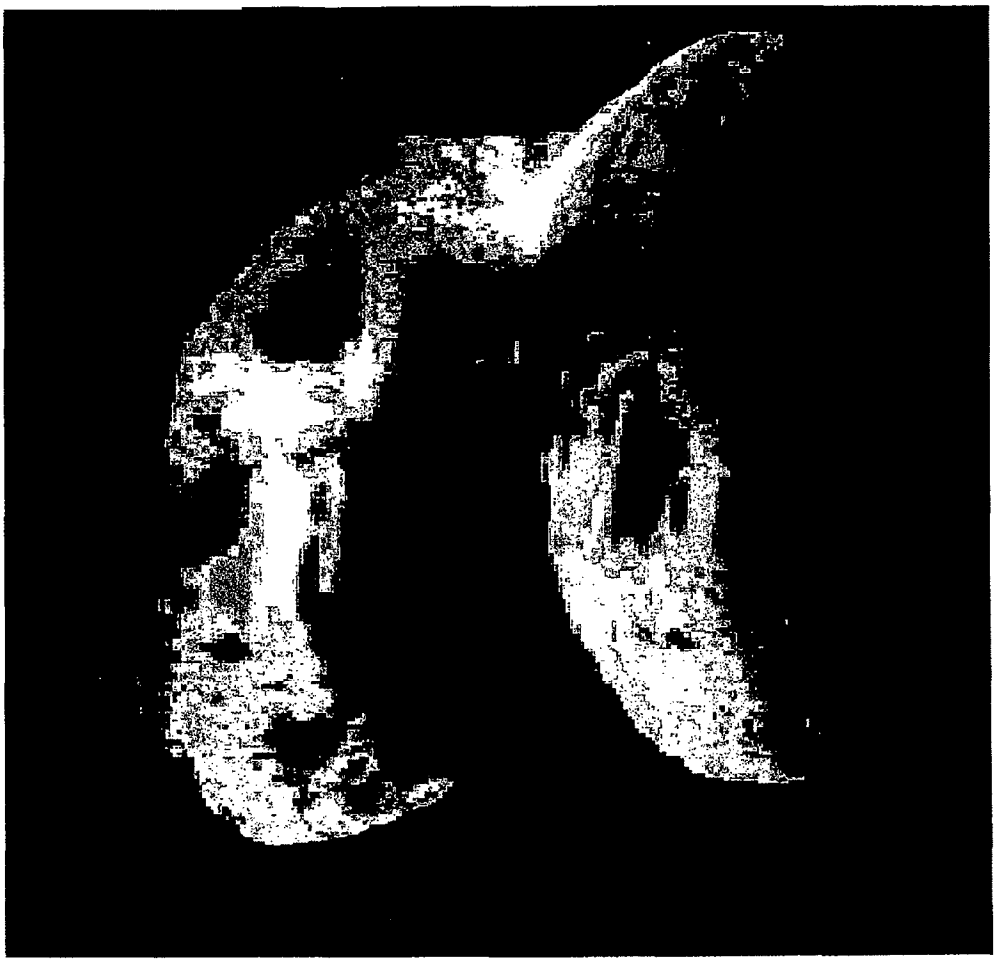


Fig. 2

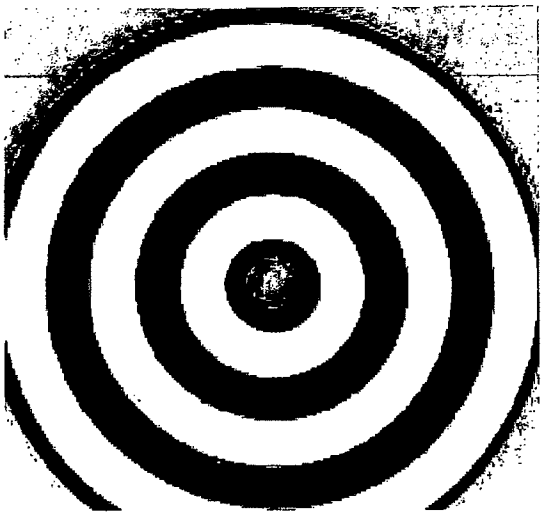


Fig. 3

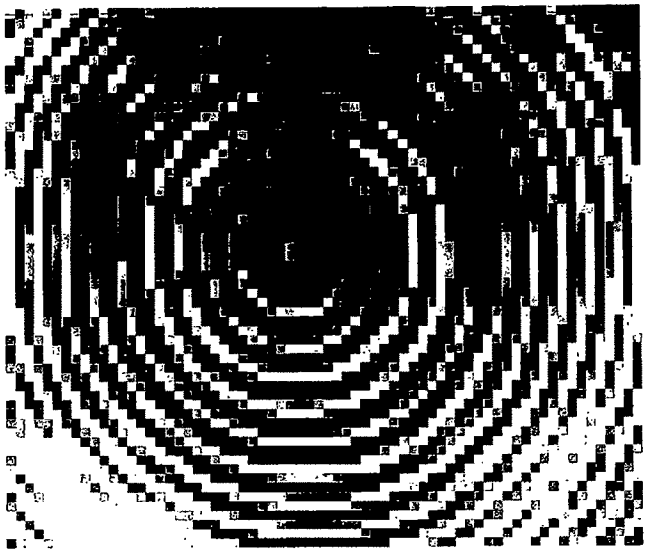


Fig. 4

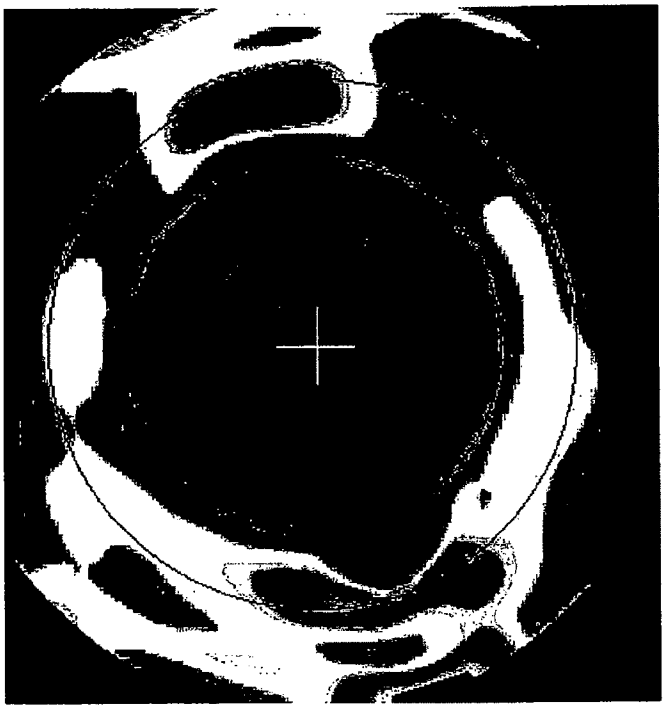


Fig. 5

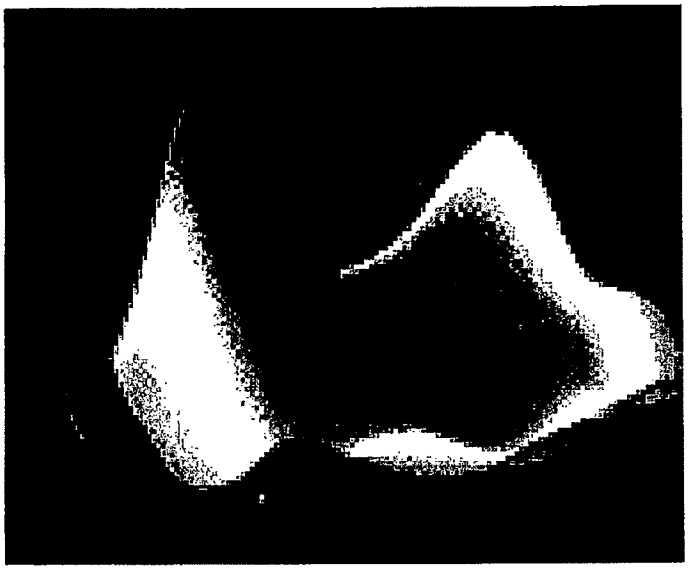


Fig. 6

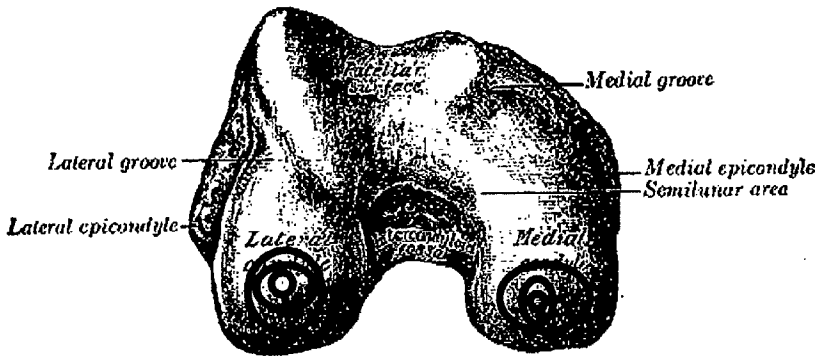

Medial groove
Lateral groove
Medial epicondyle
Semilunar area
Lateral epicondyle
Lateral
Medial

Fig. 7

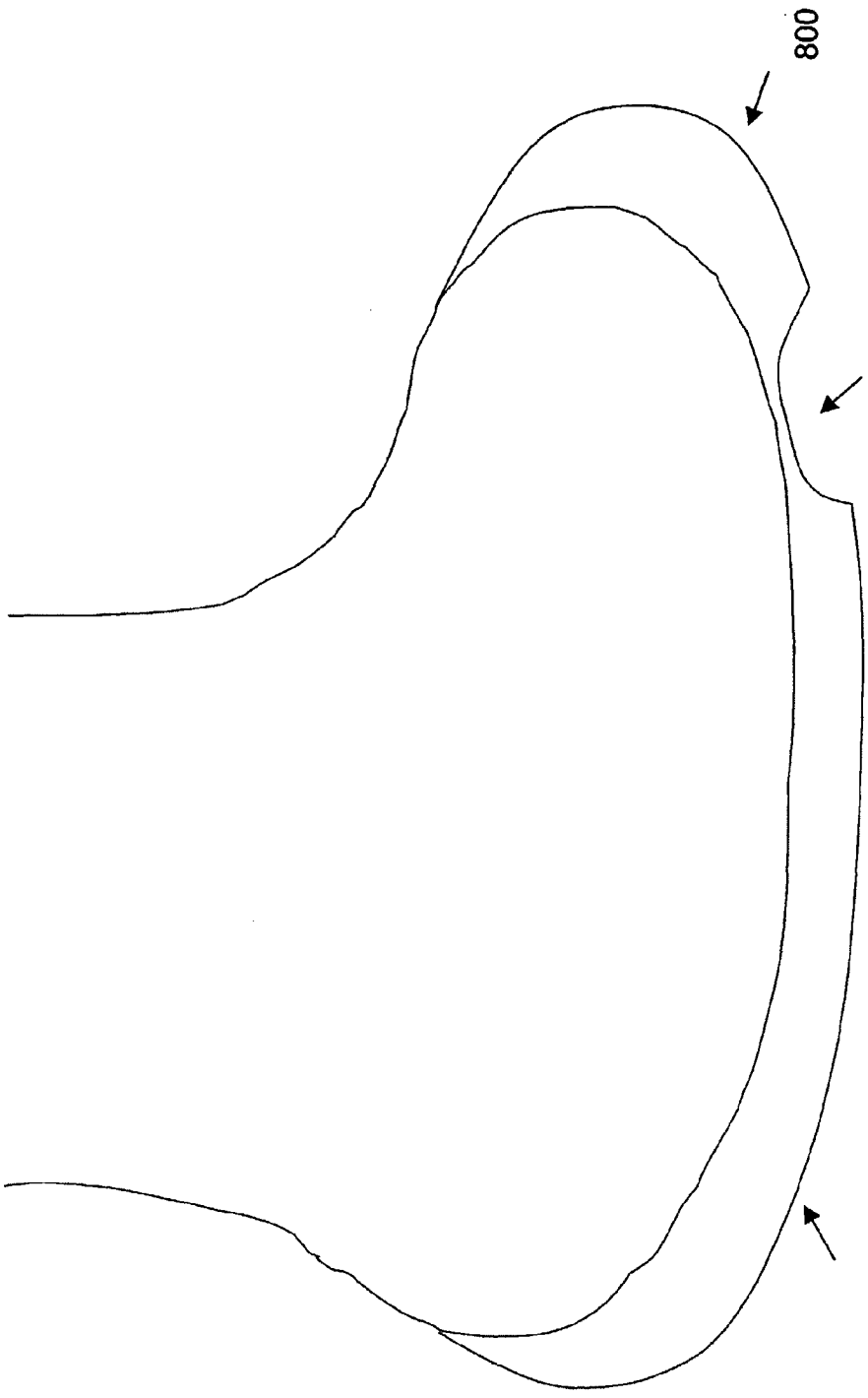


Figure 8A

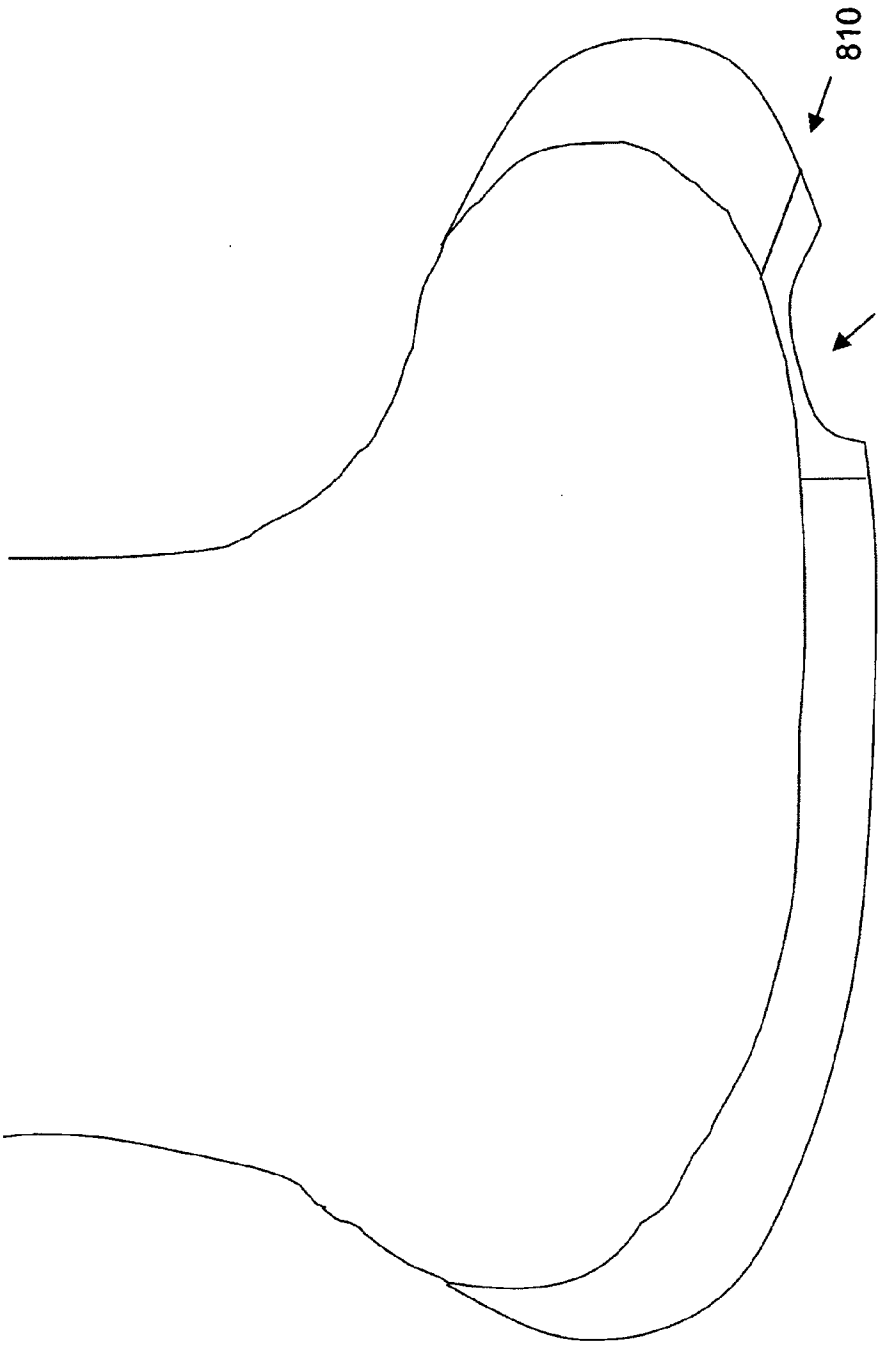


Figure 8B

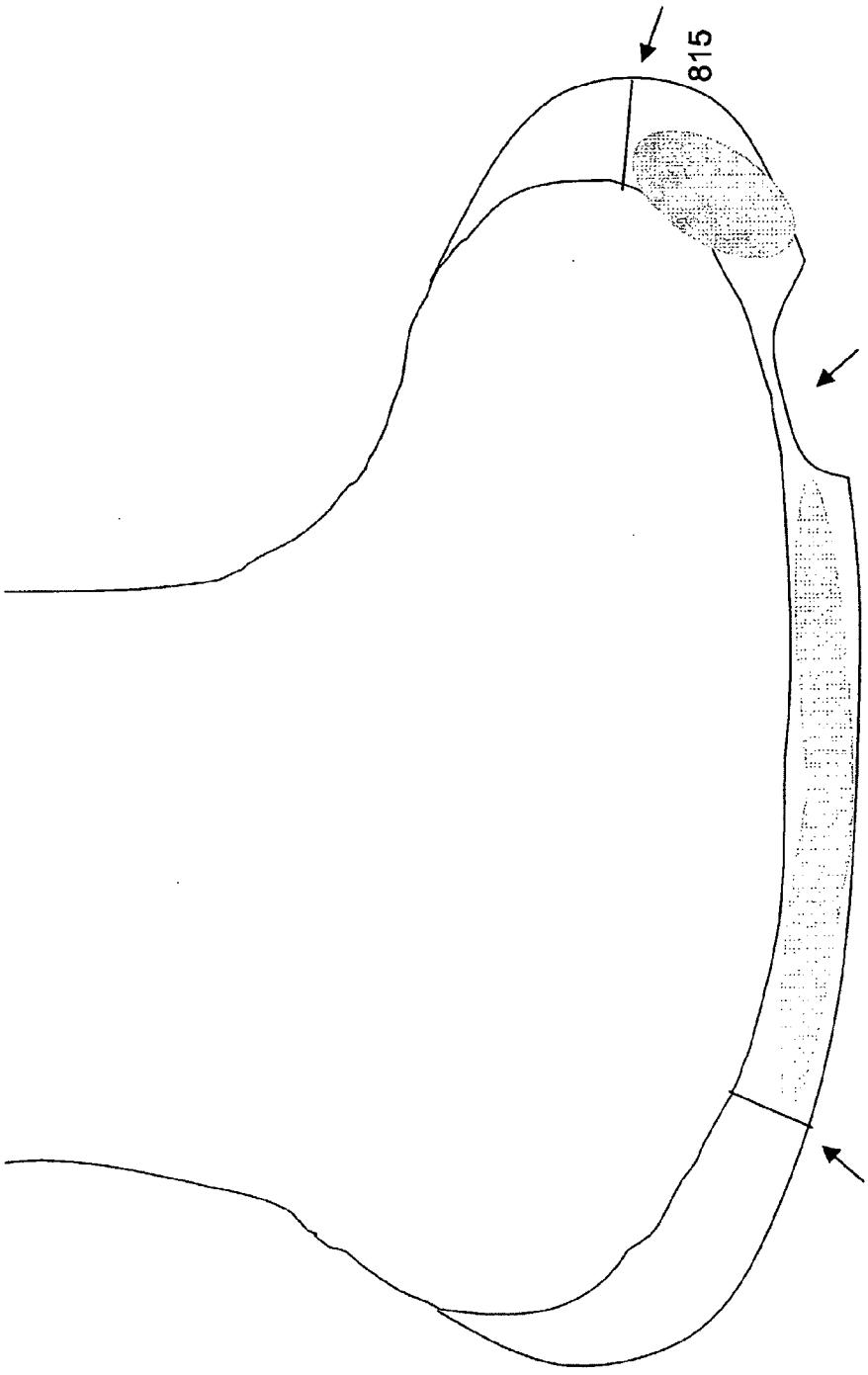


Figure 8C

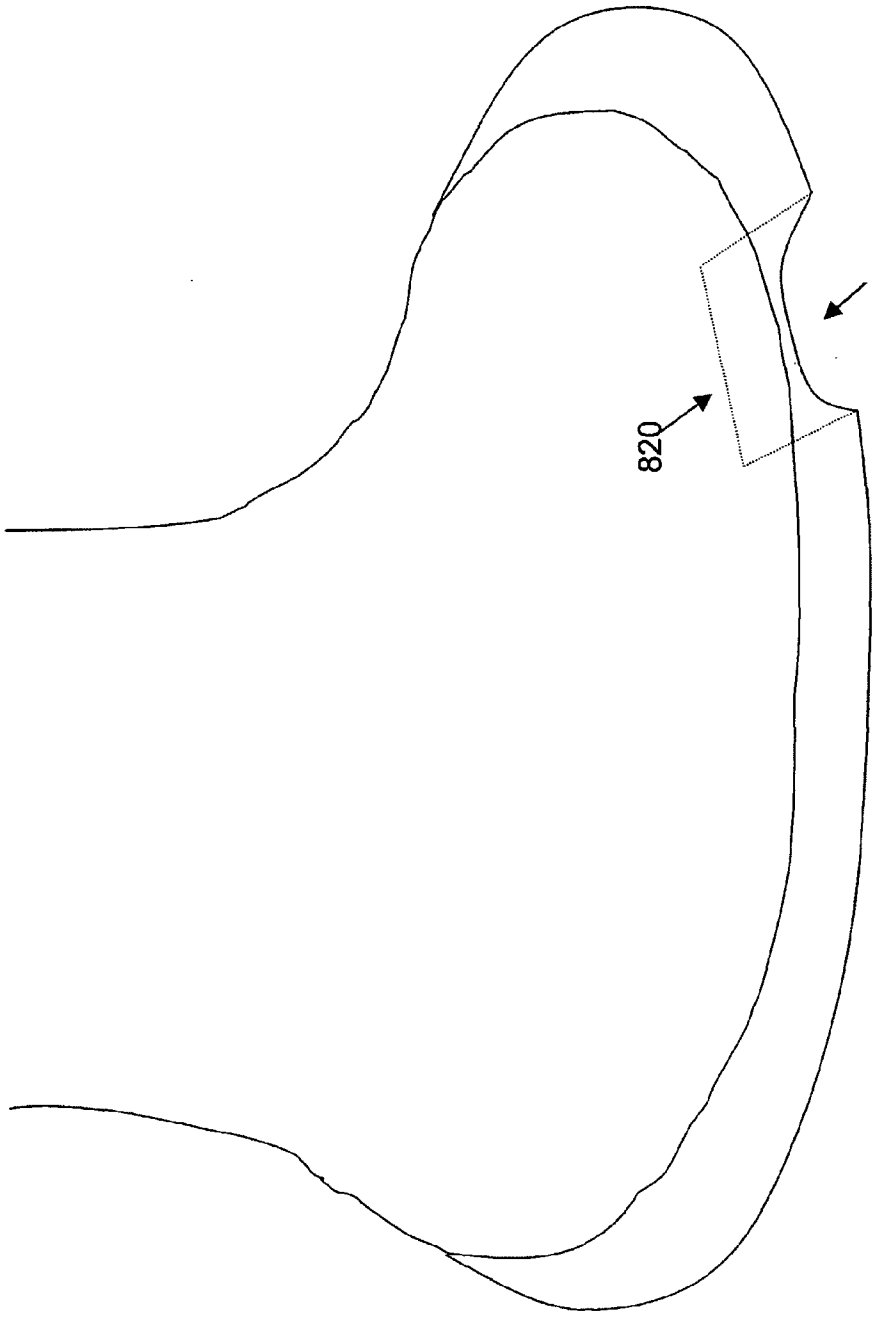


Figure 8D

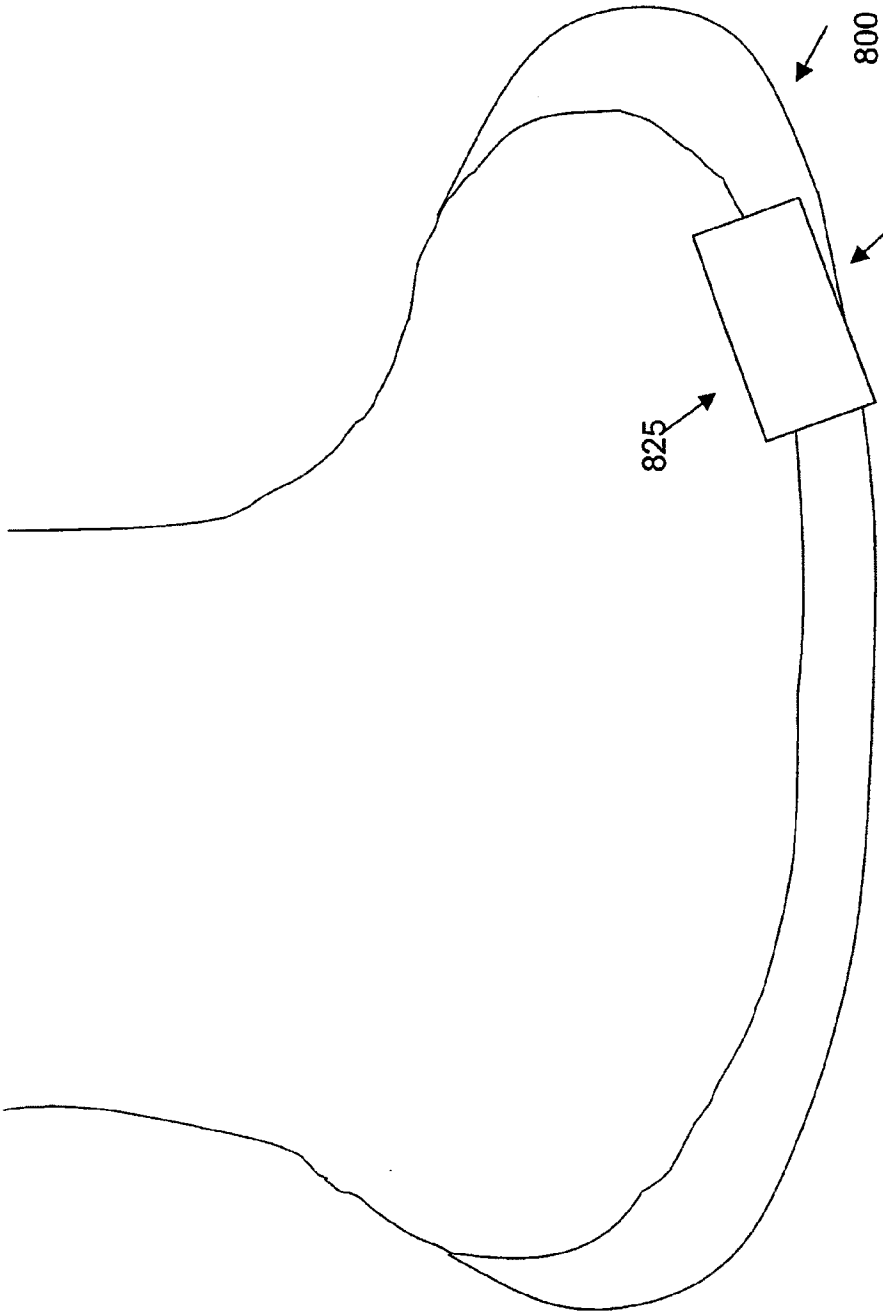


Figure 8E

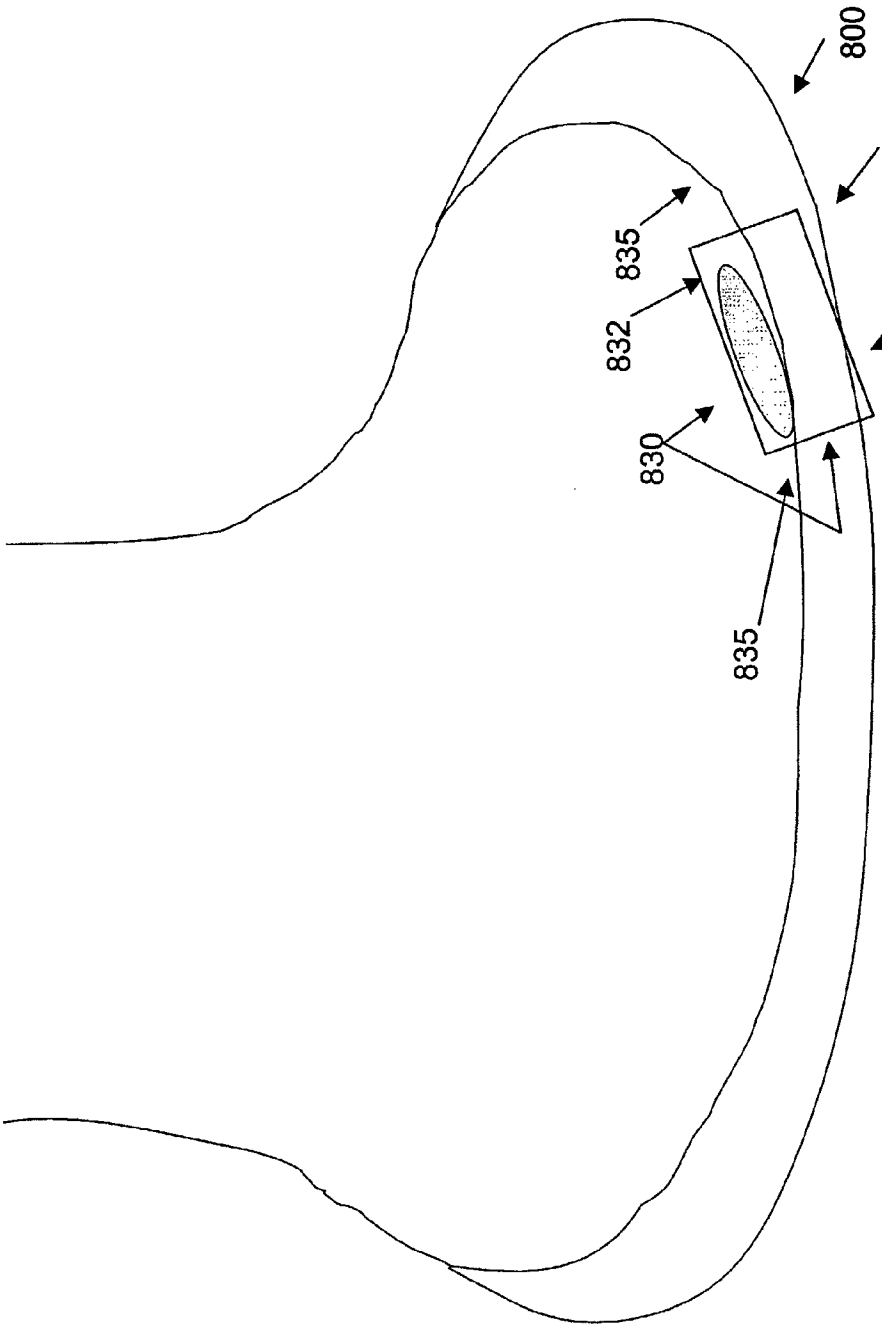


Figure 8F

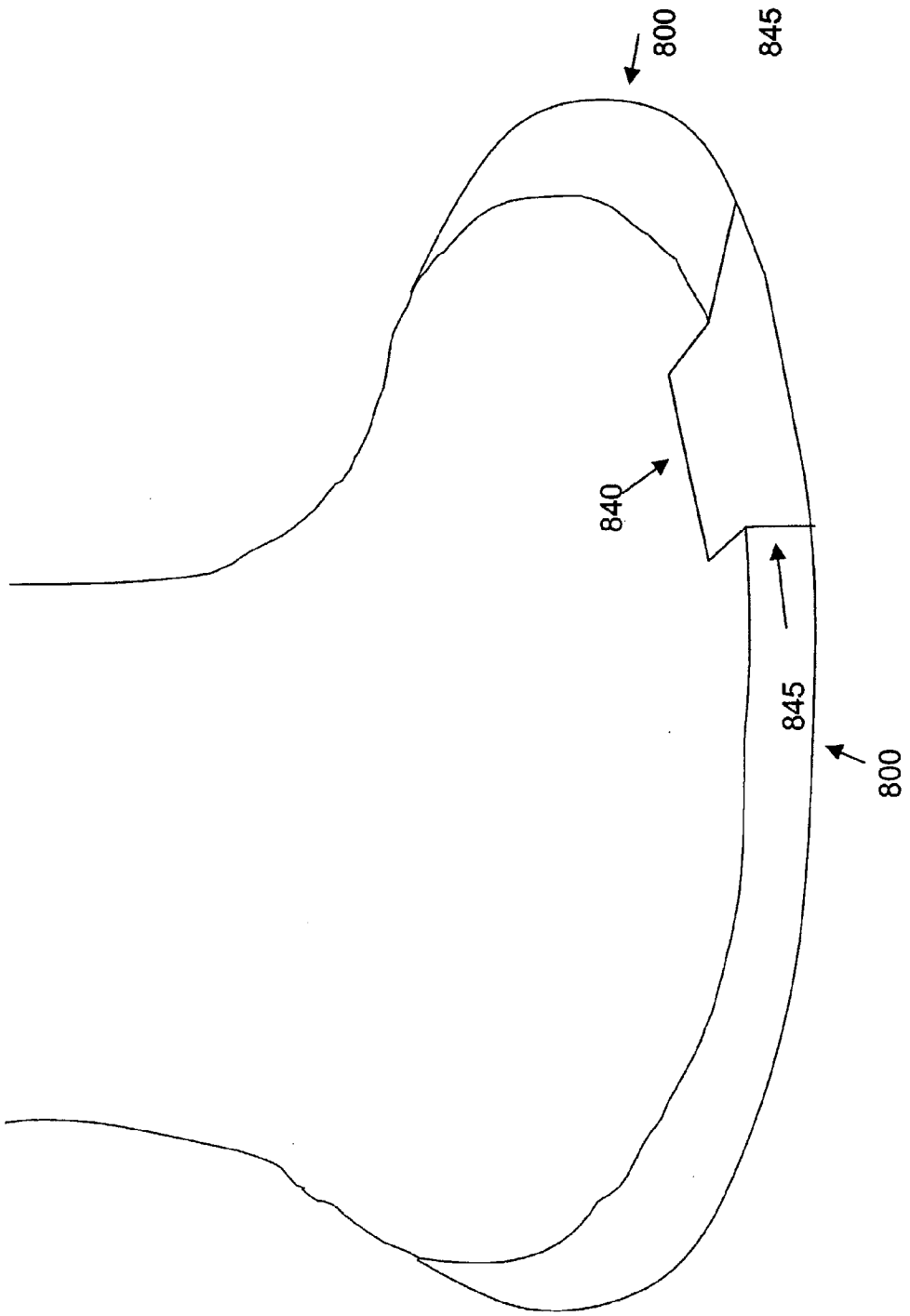


Figure 8G

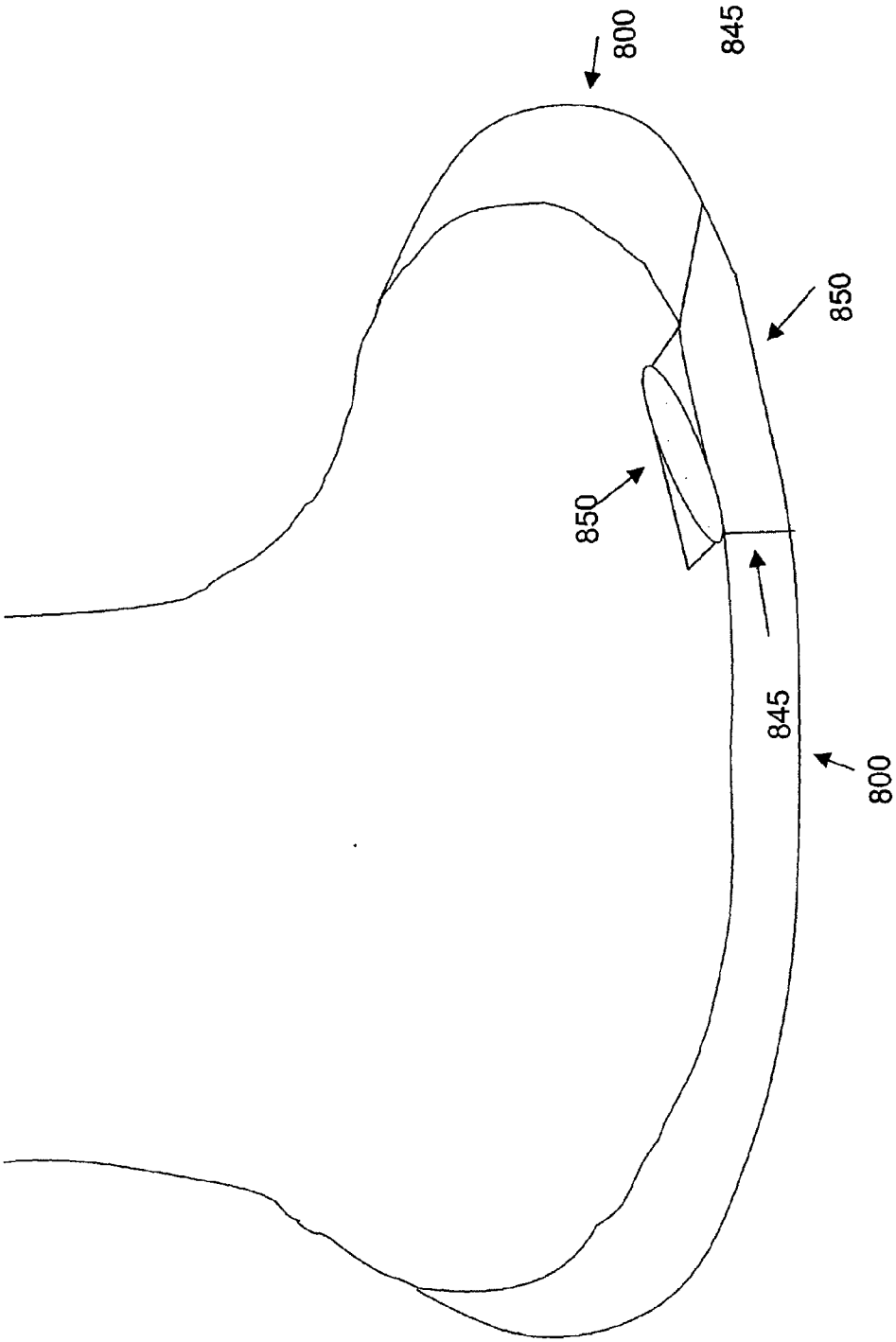


Figure 8H

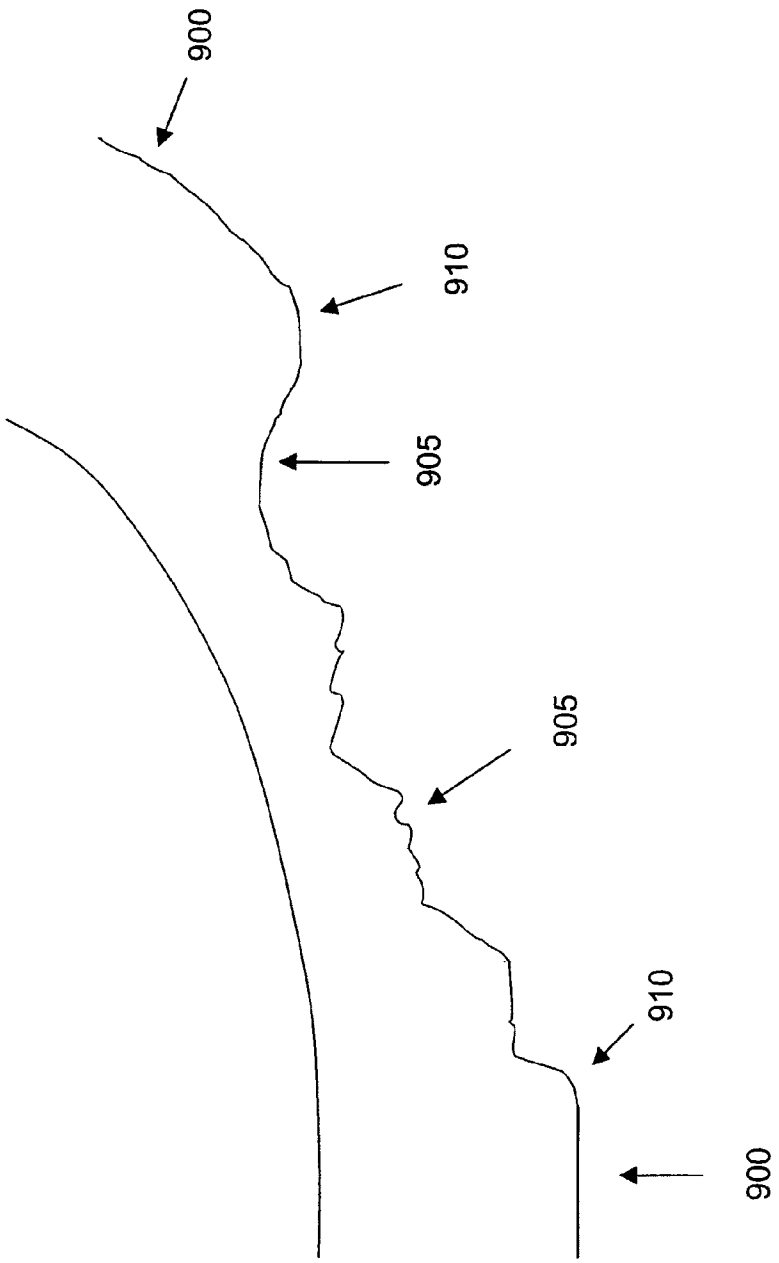


Figure 9A

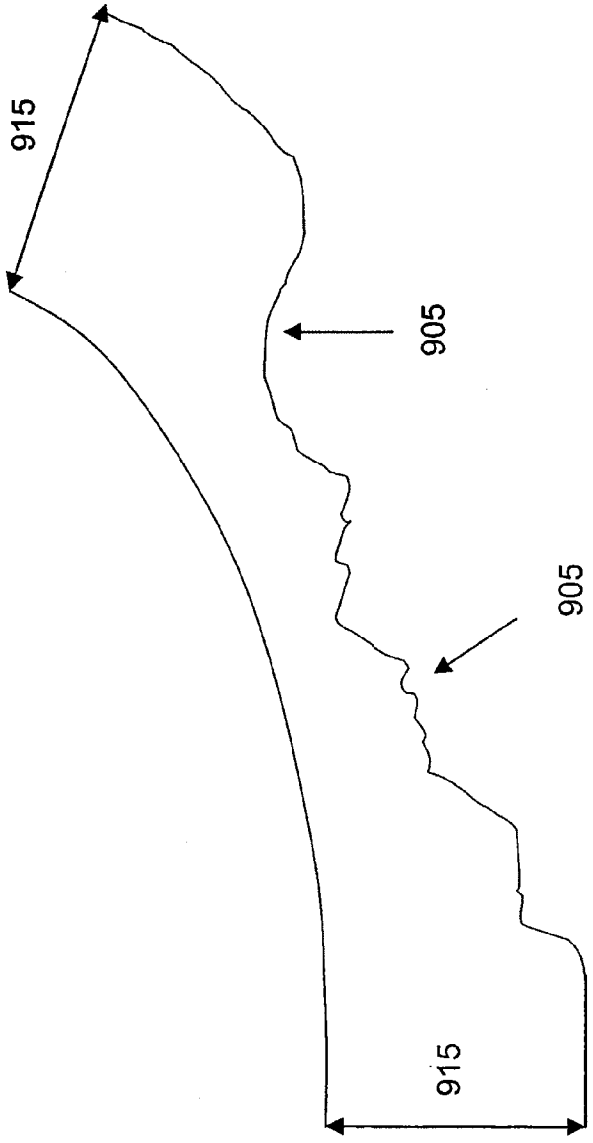


Figure 9B

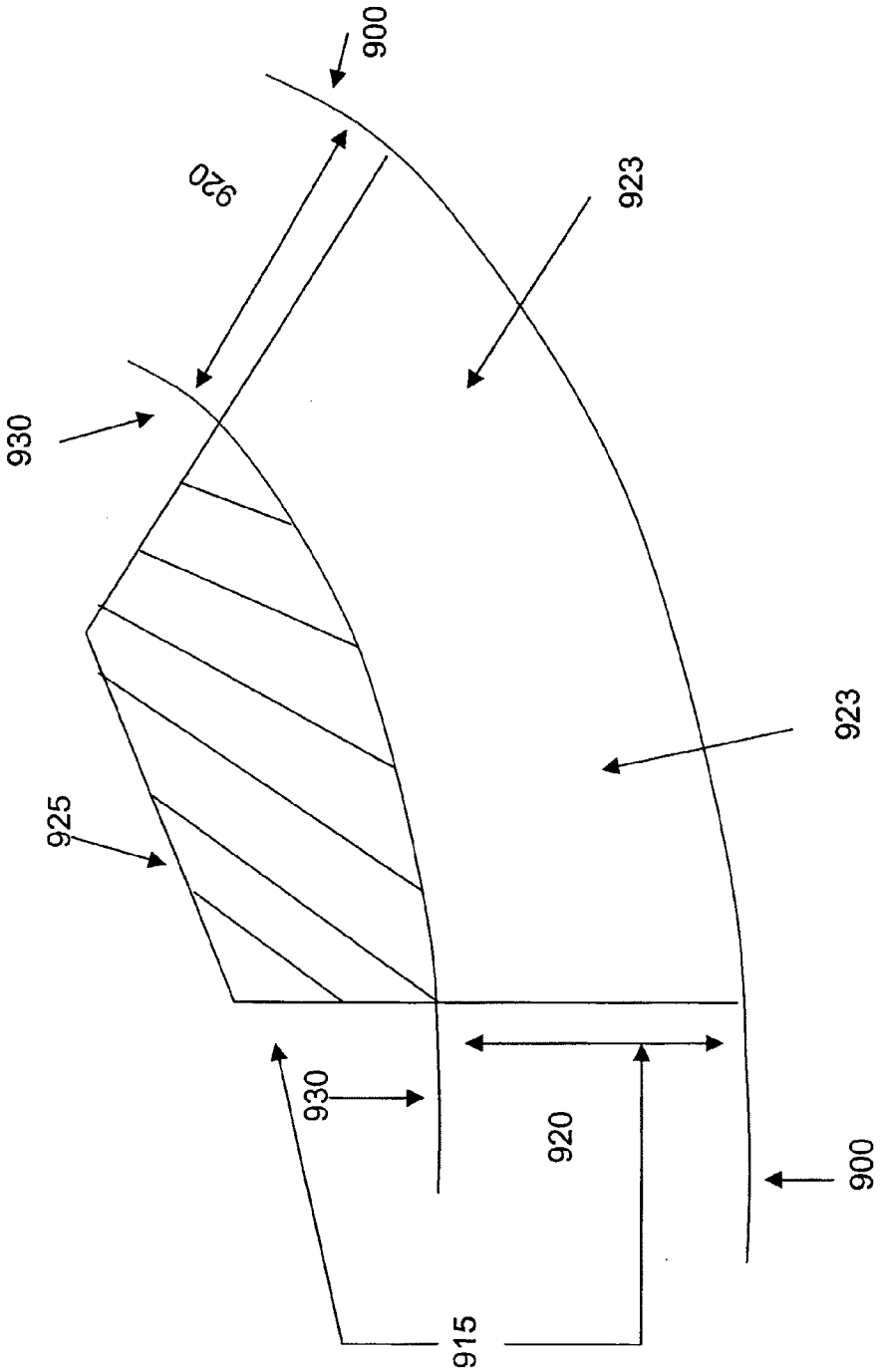


Figure 9C

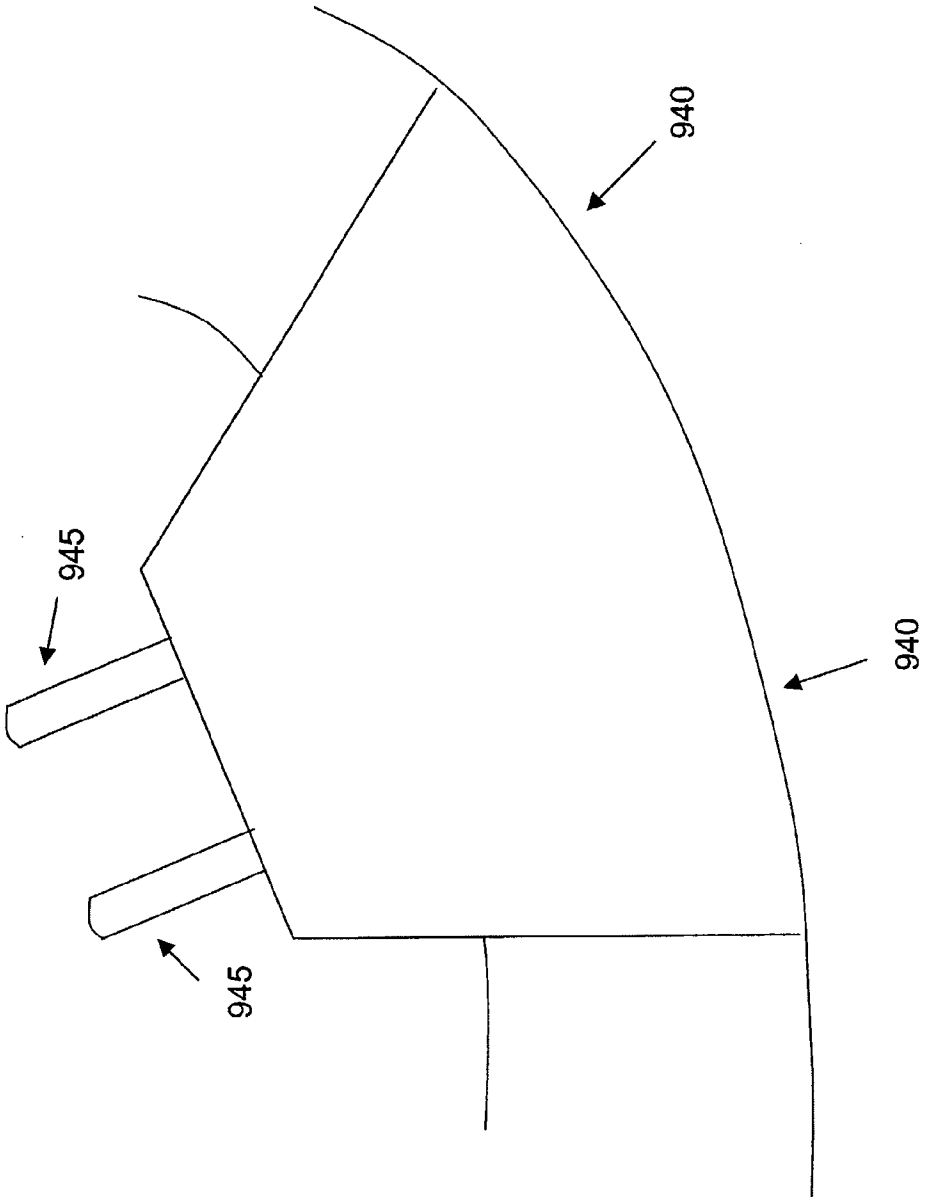


Figure 9D

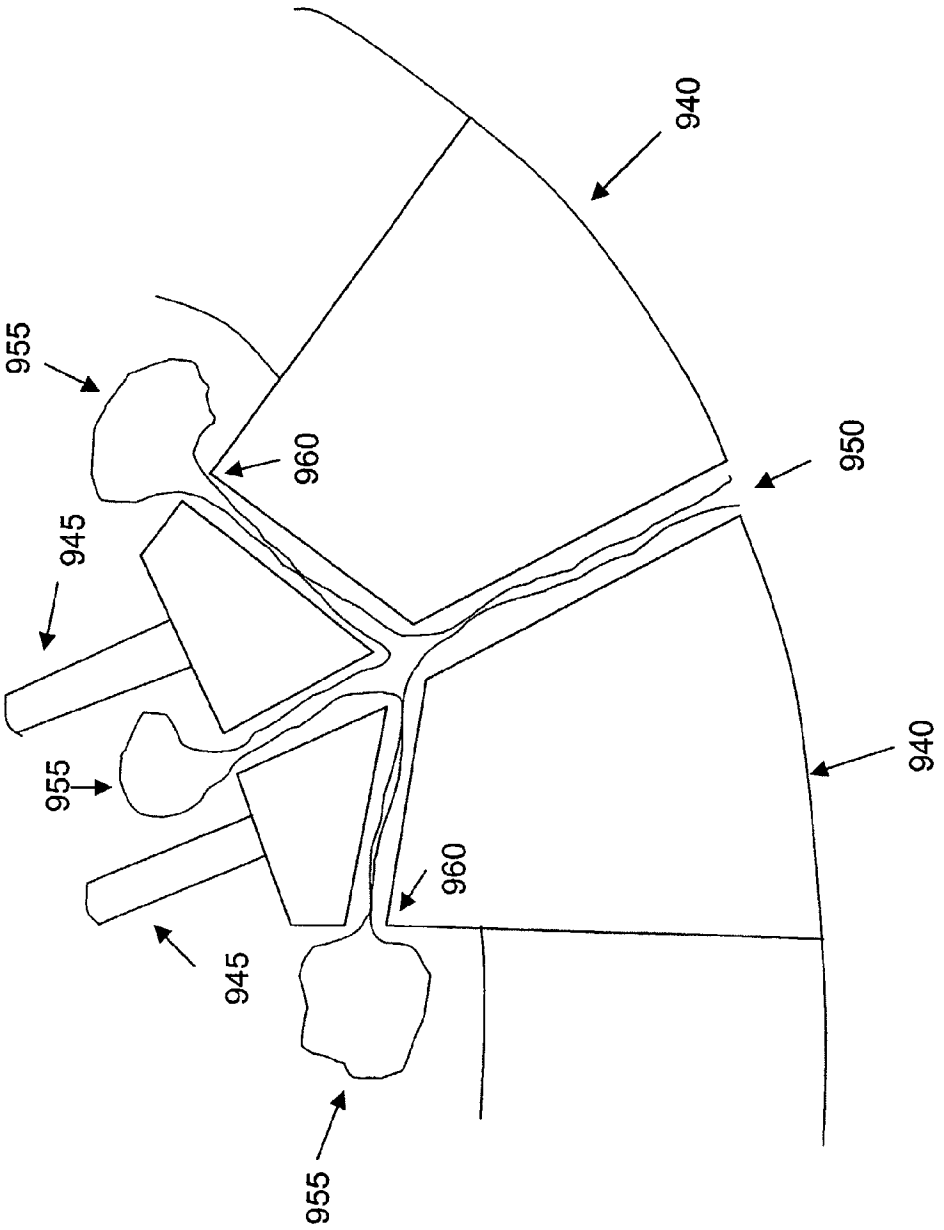


Figure 9E

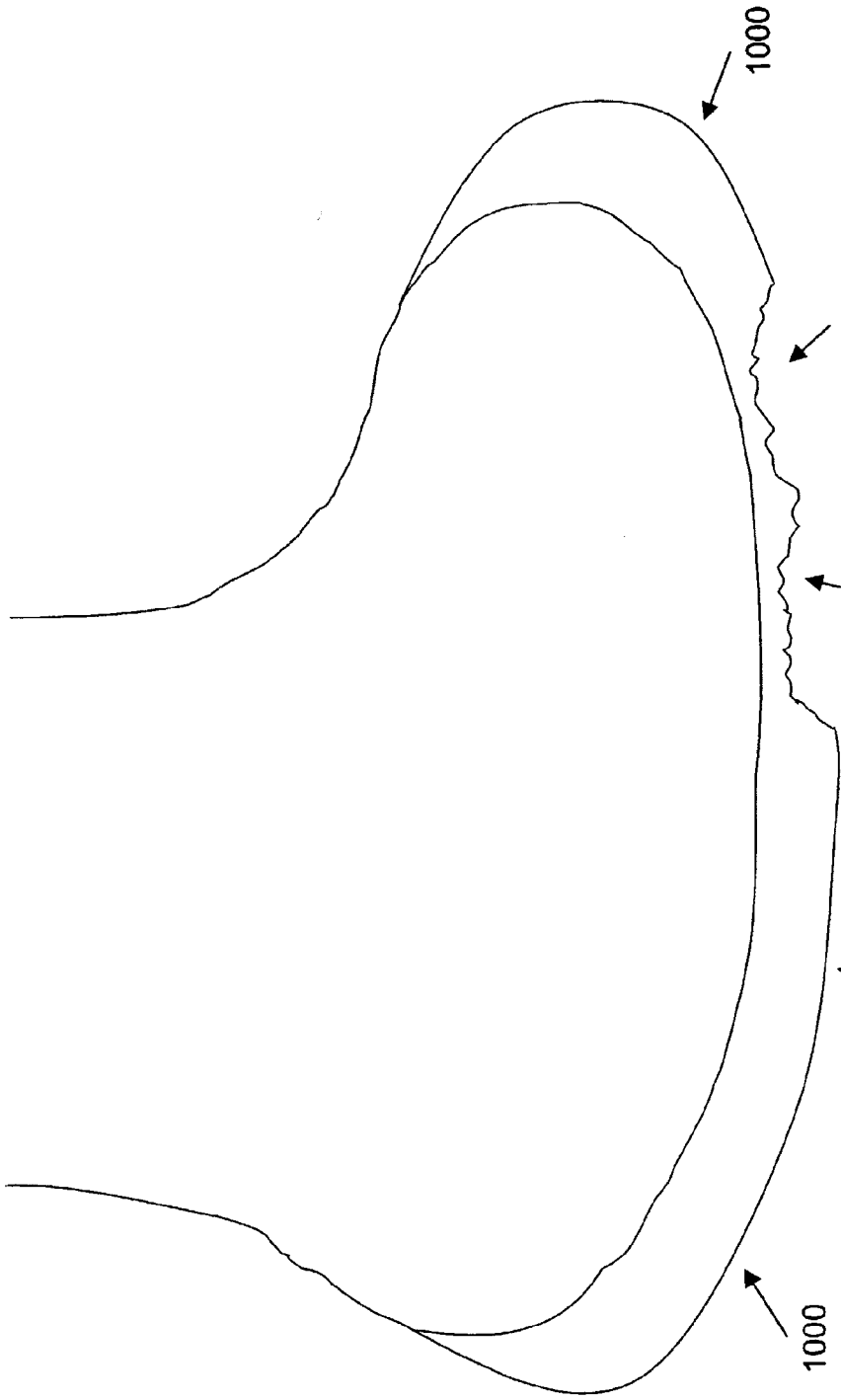


Figure 10A

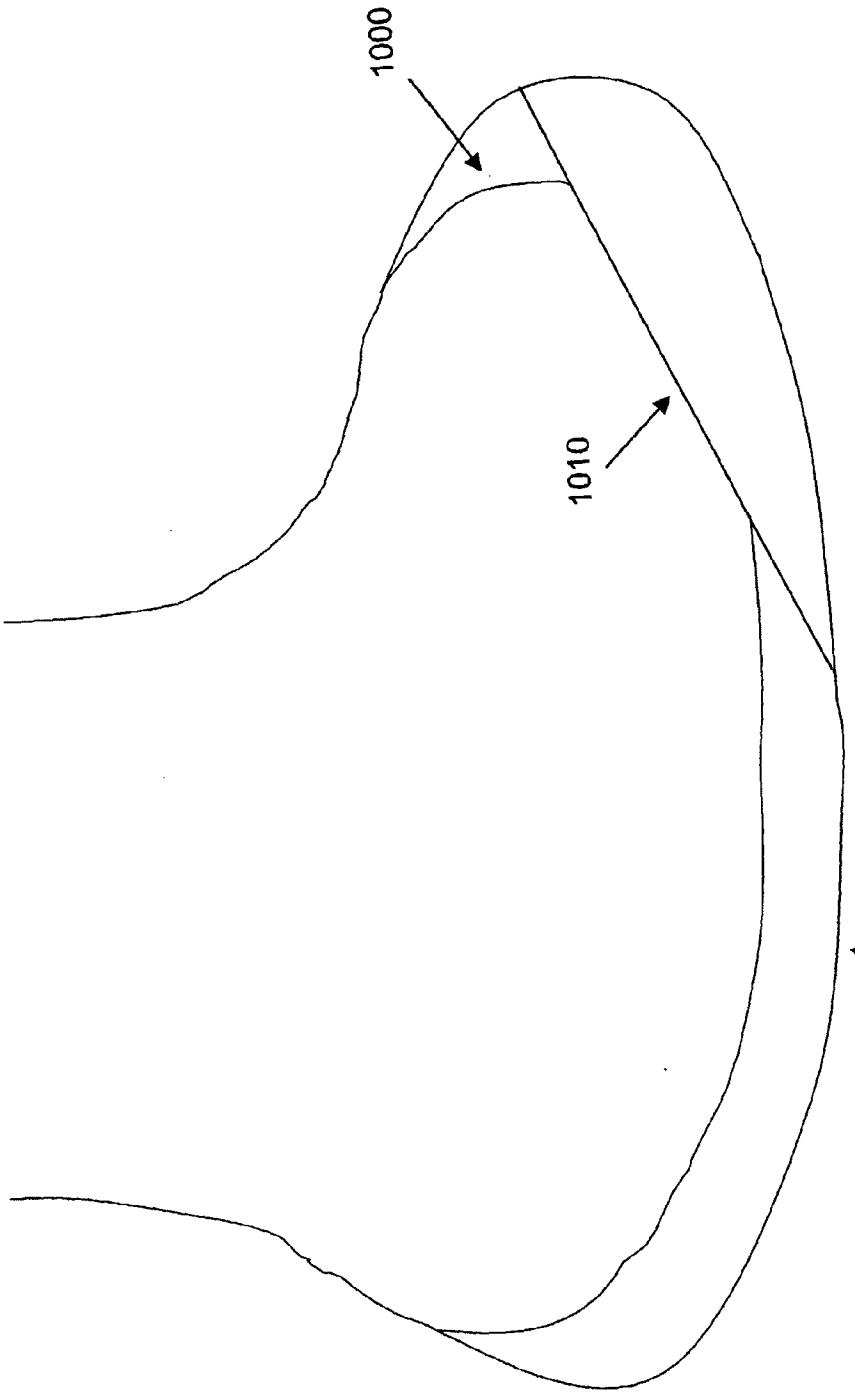


Figure 10B

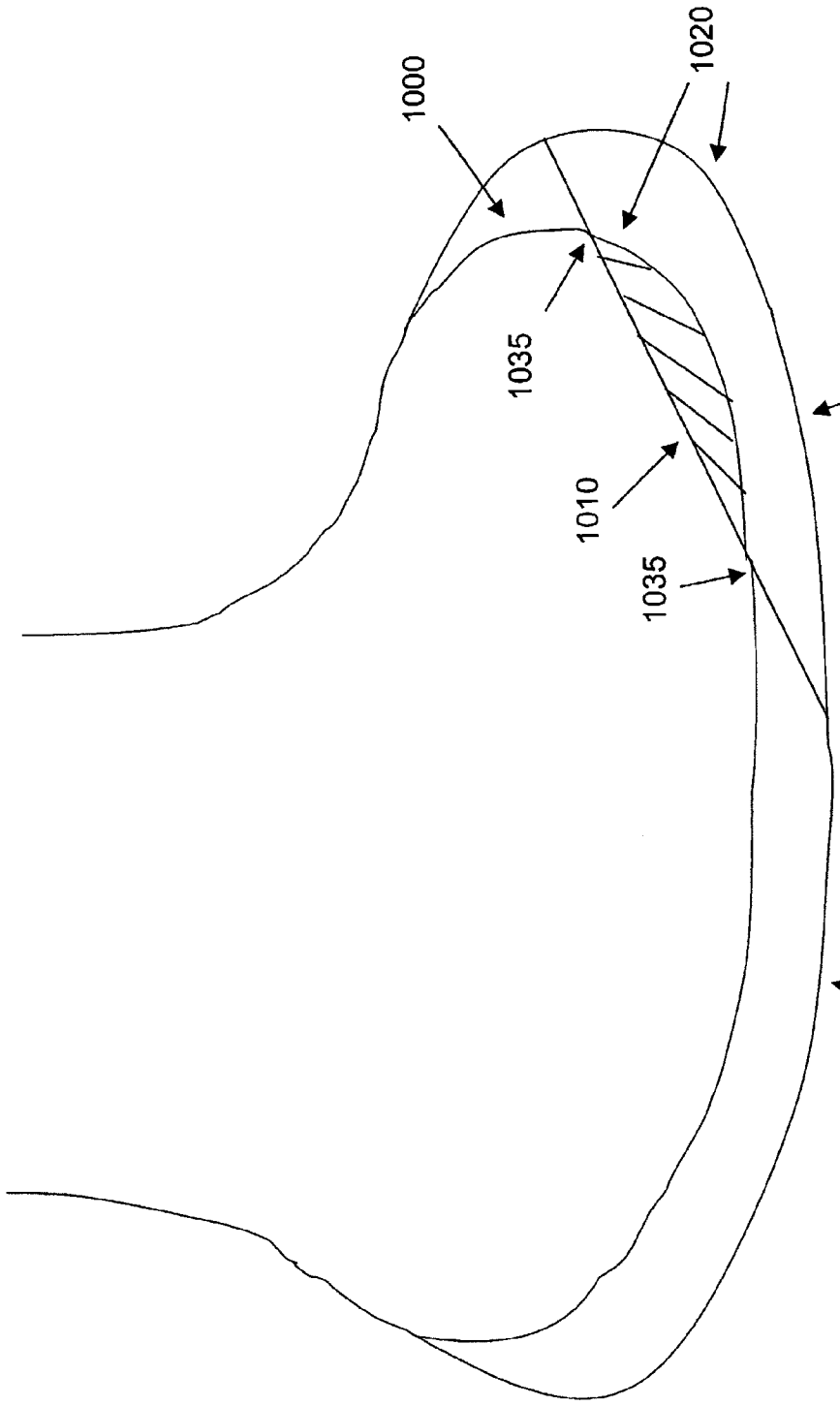
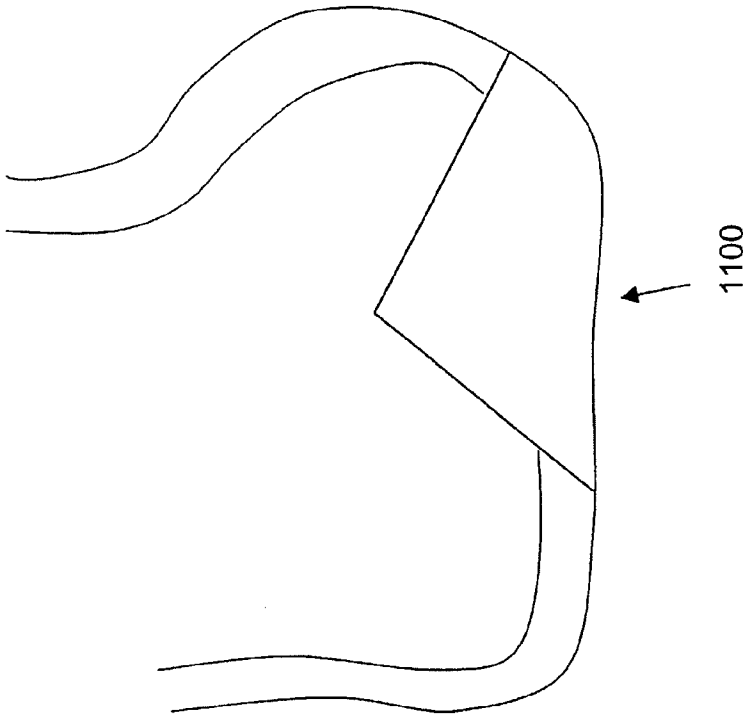


Figure 10C

Figure 11A



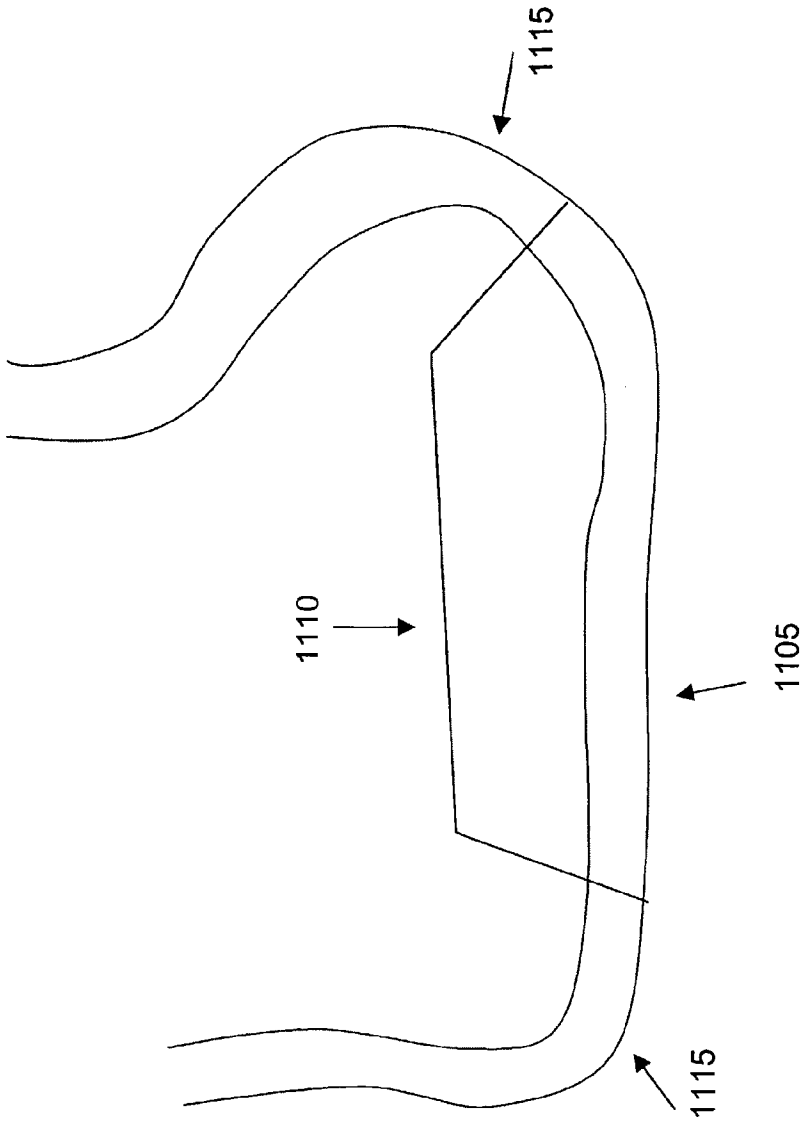


Figure 11B

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
5 December 2002 (05.12.2002)

PCT

(10) International Publication Number
WO 02/096268 A3

(51) International Patent Classification[7]: A61F 2/30

(21) International Application Number: PCT/US02/16945

(22) International Filing Date: 28 May 2002 (28.05.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/293,488	25 May 2001 (25.05.2001)	US
60/363,527	12 March 2002 (12.03.2002)	US
60/380,695	14 May 2002 (14.05.2002)	US
60/380,692	14 May 2002 (14.05.2002)	US

(63) Related by continuation (CON) or continuation-in-part (CIP) to earlier applications:

US	60/293,488 (CIP)
Filed on	25 May 2001 (25.05.2001)
US	60/363,527 (CIP)
Filed on	12 March 2002 (12.03.2002)
US	60/380,695 (CIP)
Filed on	14 May 2002 (14.05.2002)
US	60/380,692 (CIP)
Filed on	14 May 2002 (14.05.2002)

(71) Applicant *(for all designated States except US)*: **IMAGING THERAPEUTICS** [US/US]; 1720 South Amphlett Boulevard, Suite 240, San Mateo, CA 94402 (US).

(72) Inventors; and

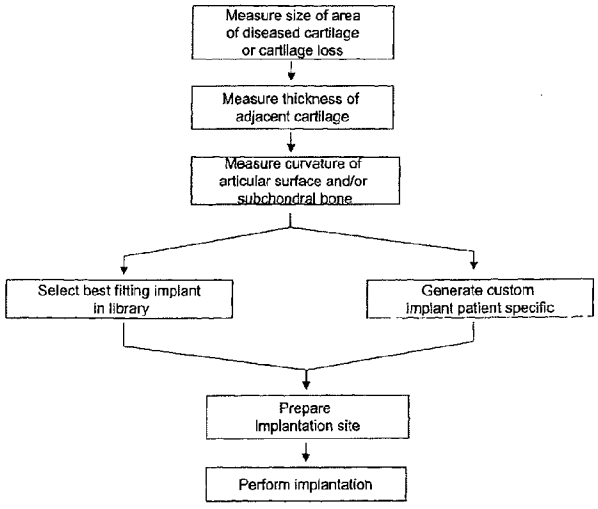
(75) Inventors/Applicants *(for US only)*: **LANG, Philipp** [DE/US]; 36 Fairlawn Lane, Lexington, MA 02420 (US). **LINDER, Barry** [US/US]; 29 Bluehaven Court, Danville, CA 94506 (US). **STEINES, Daniel** [DE/US]; 3619 Park Boulevard, Palo Alto, CA 94306 (US).

(74) Agents: **PASTERNAK, Dahna, S.** et al.; Robins & Pasternak LLP, 545 Middlefield Road, Suite 180, Menlo Park, CA 94025 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG,

[Continued on next page]

(54) Title: METHODS AND COMPOSITIONS FOR ARTICULAR RESURFACING



(57) Abstract: Methods and compositions for producing articular repair materials (825) and for repairing an articular surface (800). In particular, methods for providing articular replacement material (825), the method comprising the step of producing articular replacement material (825) of selected size, curvature and/or thickness are provided. Also provided are articular surface repair systems (830) designed to replace a selected area cartilage (805), for example, a system (830) comprising at least one solid, non-pliable component and an external surface having near anatomic alignment to the surrounding structures.

WO 02/096268 A3

SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(84) **Designated States** *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

(88) **Date of publication of the international search report:**
31 July 2003

(15) **Information about Correction:**
Previous Correction:
see PCT Gazette No. 15/2003 of 10 April 2003, Section II

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/16945

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :A61F 2/30
US CL : 623/13.12, 23.61
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 623/13.1, 13.12, 13.17, 13.18, 23.61

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 4,055,862 A (FARLING) 01 November 1977, see entire document.	1-5 --- 24-28,46-48,57-61,63- 65,67-71
X --- Y	US 5,067,964 A (RICHMOND et al) 26 November 1991, see entire documnet.	1-4, 24-27 --- 5,21-23,28,38,40-43,46-48,57-61, 63-65,67-71

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 23 SEPTEMBER 2002	Date of mailing of the international search report 26 MAR 2003
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer RALPH A. LEWIS Telephone No. (703) 308-0770

Form PCT/ISA/210 (second sheet) (July 1998)★

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/16945

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X ----- Y	US 5,306,311 A (STONE et al) 26 April 1994, see entire document.	1-4, 24-27 ------- 5,21-23,28, 38,40-43,46-48,57-61, 63-65,67-71
X ----- Y	US 5,632,745 A (SCHWARTZ) 27 May 1997, see entire document.	1-4, 24-27 ------- 5,21-23,28, 38,40-43,46-48,57-61,63-65,67-71
X	US 6,120,541 A (JOHNSON) 19 September 2000, see entire document.	1-5, 24-27

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/16945

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 6-20, 29-37, 39, 44-45, 49-56, 62, 66, and 72-74
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.